A Phase 2, Multicenter, Open-Label, Extension Study to Evaluate the Safety and Tolerability of AK002 in Patients with Eosinophilic Gastritis and/or Eosinophilic Duodenitis (formerly referred to as Eosinophilic Gastroenteritis)

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Clinical Research Protocol AK002-003X

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	Amendment 3:	18 March 2019
	Amendment 4:	23 May 2019
	Amendment 5:	24 September 2019
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	Amendment 7:	**03 March 2021**
Investigational Product	AK002 (lirentelimab)	
Study Phase	2	
Sponsor	Allakos Inc. 975 Island Drive, Suite 201, Redwood City, CA 94065 USA	
Medical Monitor	Name: [redacted], MD, PhD Telephone: [redacted] E-mail: [redacted]	

Approval: [redacted]

03-Mar-2021 | 11:43 PST

[redacted], MD, PhD, [redacted] — Date

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Investigator Protocol Agreement

I have read the protocol specified below. In my formal capacity as Principal Investigator, my duties include ensuring the safety of the study 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 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 accepted Good Clinical Practice (GCP) principles and to abide by the terms of this protocol.

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Investigator's Name (printed): _____

Signature: _____

Date: _____

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List of Abbreviations

AC	Allergic conjunctivitis
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse Event
AEC	Absolute Eosinophil Count
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
Anti-HBc	Anti-Hepatitis B core antibody
AST	Aspartate aminotransferase
AUC	Area under the curve
AV	Adelphi Values
BMI	Body Mass Index
BQL	Below quantifiable limit
BUN	Blood urea nitrogen
C	Centigrade
CBC	Complete blood count
CFR	Code of Federal Regulations
cm	Centimeter
COVID-19	Coronavirus disease 2019
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CU	Chronic Urticaria
DSQ	Dysphagia Symptom Questionnaire
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture (system)
EG	Eosinophilic gastritis
EGD	Esophago-Gastro-Duodenoscopy
EGE	Eosinophilic gastroenteritis
EGID	Eosinophilic gastrointestinal disorders
EoD	Eosinophilic duodenitis
EoE	Eosinophilic Esophagitis

Eos	Eosinophil
ET	Early termination
Ext	Extension
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practices
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HES	Hypereosinophilic Syndrome
HIPAA	Health Insurance Portability and Accountability Act
hpf	High power field
ICF	Informed consent form
ICH	International Conference on Harmonisation
IgE	Immunoglobulin E
IgG1	Immunoglobulin G1
IND	Investigational New Drug
IRB	Institutional Review Board
IRR	Infusion related reaction
ISM	Indolent systemic mastocytosis
ISR	Injection Site Reaction
IRT	Interactive response technology (system)
IV	Intravenous
kg	Kilogram
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
Lymph	Lymphocyte
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mIU	Milli-international unit
MTD	Maximum tolerated dose
NaCl	Sodium chloride

NCI	National Cancer Institute
NCS	Not clinically significant
NOAEL	No-observed-adverse-effect level
PCP	Primary Care Physician
PD	Pharmacodynamic(s)
PE	Physical Examination
PGIC	Patient Global Impression of Change
PID	Patient identification number
PP	Per protocol
PK	Pharmacokinetic(s)
SAE	Serious adverse event
SF-36	Short-form health survey
Siglec-8	Sialic acid-binding, immunoglobulin-like lectin-8
SOC	Standard of care
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TSS	Total symptom score
TSS8	Total symptom score on 8 symptom intensity scores
µL	Microliter
ULN	Upper limit of normal
WHO	World Health Organization
w/v	Weight/volume

1. Protocol Synopsis

Study Title	A Phase 2, Multicenter, Open-Label, Extension Study to Evaluate the Safety and Tolerability of AK002 in Patients with Eosinophilic Gastritis and/or Eosinophilic Duodenitis (formerly referred to as Eosinophilic Gastroenteritis)
Sponsor	Allakos Inc., 975 Island Drive, Suite 201, Redwood City, CA 94065 USA
Number of Sites	Approximately 20 clinical centers in the United States
Nonclinical Background	AK002 is a humanized non-fucosylated immunoglobulin G1 (IgG1) monoclonal antibody directed against Siglec-8, a member of the CD33-related family of sialic acid-binding, immunoglobulin-like lectins (Siglecs). Siglec-8 has a restricted tissue distribution, expressed selectively on the surface of mature eosinophils and mast cells, but not in early precursors of these cell populations. Binding of AK002 to Siglec-8 induces a signal which leads to apoptosis of eosinophils and broad inhibition of mast cells. In addition, there is rapid and marked depletion of eosinophils in the blood due to antibody-dependent cellular cytotoxicity (ADCC).
Clinical Background	AK002, administered as an intravenous infusion, has been previously tested in healthy volunteers and in patients with indolent systemic mastocytosis (ISM), chronic urticaria (CU), severe allergic conjunctivitis (AC) mast cell gastritis, and eosinophilic gastritis (EG) and/or eosinophilic duodenitis (EoD), which was referred to as eosinophilic gastroenteritis in previous versions of this protocol. Multiple doses of 3 mg/kg have been given to patients with ISM, CU, severe AC, and EG/EoD. In these studies, patients reported improvements in disease symptoms with AK002 pharmacodynamic (PD) activity being observed for prolonged periods of time and pharmacokinetic (PK) parameters demonstrating a half-life amendable to administration every 4 weeks. To date, over 300 healthy volunteers and patients with ISM, CU, severe AC, EG/EoD, EoE, and mast cell gastritis have been enrolled in clinical studies. In general, AK002 has been well tolerated. The most common treatment-emergent adverse events (TEAE) observed were infusion-related reactions (IRR). Most IRR were mild to moderate; 2 IRR were classified as serious but resolved within 24 hours. Transient lymphopenia was observed after infusion of AK002 but was not associated with any clinical consequence, and lymphocytes recovered within 24 hours. A sustained depletion of eosinophils was observed that is consistent with the mechanism of action of AK002. In the randomized, double-blind, placebo-controlled, Phase 2 study of AK002 in 65 patients with EG and/or EoD, patients were randomized to receive monthly doses of placebo, low dose AK002 (0.3, 1, 1, and 1 mg/kg), or high dose AK002 (0.3, 1, 3, and 3 mg/kg) in a 1:1:1 ratio (Dellon, 2020).

Clinical Background cont.	All primary and secondary endpoints were met in the study. There was a 97% and 92% mean reduction in eosinophils in the stomach/duodenum on the high dose and low dose, respectively, versus 10% increase on placebo ($p<0.0001$). The reduction of eosinophils was associated with a statistically significant reduction in total symptom score (TSS) on 8 symptom intensity scores (TSS8) of 58% in the high dose group and 49% in the low dose group versus 24% reduction in the placebo group ($p=0.0012$ and $p=0.015$, respectively). Improvement in symptoms was observed within 24 hours of the first dose of study drug. In addition, 70% of high dose treated patients and 68% of low dose treated patients were treatment responders (defined as >30% improvement in TSS and >75% reduction from baseline in tissue eosinophils) versus 5% for placebo treated patients ($p<0.0001$).
Target Disease Background and Rationale	EG and/or EoD represent what are believed to be rare types of eosinophilic gastrointestinal disorders (EGID) that are characterized by chronic, often severe inflammation due to patchy or diffuse infiltration of eosinophils into layers of the stomach, small intestine, or both. (Prussin, 2014; Reed, 2015; Zhang, 2017). The diagnosis is made based on clinical presentation (gastrointestinal symptoms) combined with increased tissue eosinophils in biopsy specimens from the stomach and/or duodenum without any other cause for the eosinophilia. Involvement of the small intestine is typically assessed by performing duodenal biopsies using an esophago-gastro-duodenoscopy (EGD) and has been referred to as eosinophilic gastroenteritis or eosinophilic enteritis though eosinophilic duodenitis (EoD) is more accurate. The gastrointestinal symptoms are believed to be due to the release of inflammatory mediators from activated eosinophils, and likely, mast cells. Symptoms that are often severe and debilitating commonly include abdominal pain, nausea, bloating, early satiety, loss of appetite, abdominal cramping, vomiting, diarrhea, and weight loss (Alhmoud, 2016; Lopez-Medina, 2015; Mansoor, 2017; Reed, 2015). Jensen (2016) estimated the prevalence of EG and EoD to be 6.3/100,000 and 8.4/100,000, respectively (for patients from 1 to 64 years of age). Mansoor (2017) estimated the overall prevalence of EG to be 5.1/100,000 persons. Patients may also have concomitant atopic diseases like food allergy, asthma, and atopic dermatitis, which further impact quality of life and contribute to health care costs. Additionally, 8% to 10% of patients have concomitant eosinophilic esophagitis (EoE) (Jensen, 2016). There are no FDA-approved treatments for EG and/or EoD. Current therapies and disease management includes dietary restriction/elimination, proton pump inhibitors (PPI), antihistamines, systemic or swallowed corticosteroids, and occasional off-label use of immunomodulatory biologics (Prussin, 2014; Reed, 2015; Zhang, 2017).

Target Disease Background and Rationale cont.	Proton pump inhibitors have little to no benefit in patients with EG and/or EoD, despite reports of providing partial benefit in some patients with EoE (Katz, 2013). Restricted/elemental diets are not effective long-term treatment as they require strict compliance and, in the case of elemental diets, are expensive and are often not reimbursed by insurance. In addition, compliance is poor and patient quality of life is greatly impacted (Bedell, 2018; Peterson, 2013; Wechsler, 2014). Corticosteroids, systemic or swallowed, have been shown to provide symptom relief but are not appropriate for long-term treatment due to numerous side effects and associated risks including adrenal insufficiency, bone demineralization, increased chance of infection, osteoporosis, behavioral issues, and weight gain. By reducing the number of blood and tissue eosinophils and inhibiting the activation of mast cells, AK002 may be useful in the treatment of patients with EG and/or EoD. This premise is supported by the Phase 2 data with AK002 that shows significant improvements in histology and symptoms in these patients. Given there are no approved therapies for these chronic and debilitating diseases, better treatment options are clearly needed to manage EG and EoD.
Rationale for Dose Selection	Based on experience with AK002 in healthy volunteers and in patients with ISM, CU, severe AC, mast cell gastritis, and EG/EoD, the proposed AK002 dose regimen is up to 26 monthly intravenous infusions of AK002. [redacted] In the double-blind, placebo-controlled Phase 2 study in patients with EG and/or EoD, 2 dose levels were evaluated: a lower dose regimen (4 monthly doses of AK002 at 0.3, 1, 1, and 1 mg/kg) and a higher dose regimen (4 monthly doses of AK002 at 0.3, 1, 3, and 3 mg/kg). [redacted] A starting dose of 1 mg/kg AK002 followed by a dose of 3 mg/kg AK002 for subsequent infusions has been chosen for the Phase 2 extension study with AK002 in patients with EG and/or EoD.
Rationale for Number of Patients	Approximately 60 patients will be enrolled in Study AK002-003X, based on the enrollment of Study AK002-003.

Study Design	This is a Phase 2, multicenter, open-label, extension study to evaluate the safety, tolerability, and efficacy of AK002 in patients with EG and/or EoD. Patients who complete Study AK002-003 will have the option to receive AK002 in an open-label manner. A patient will be categorized as having completed Study AK002-003 if 4 infusions of study drug are administered and the patient is followed through Day 113 (±3 days). Patients who were discontinued from treatment in Study AK002-003 at the recommendation of the unblinded safety monitor for high eosinophil counts prior to infusions 2, 3, or 4, will have the option to receive AK002 in an open-label manner. Patients who enroll in Study AK002-003X will receive monthly AK002 infusions for a maximum of 26 intravenous doses. During Extension Study AK002-003X, patients will maintain the same patient number that was assigned in Study AK002-003. Safety will be assessed by body weight, vital signs, symptom-directed physical examination, complete blood count (CBC) with differential, blood chemistry, urinalysis, and assessment of adverse events (AE) (including adverse events of special interest [AESI] and serious adverse events [SAE]). In addition, blood samples will be obtained for evaluation of anti-drug antibodies (ADA). The study is designed as follows: • Patients completing Study AK002-003 and wanting to enter the extension study will begin extended dosing on Day 113 of Study AK002-003 (following final assessments of Study AK002-003), which will be considered Day 1 of Study AK002-003X. If patients cannot start extended dosing within 45 days of AK002-003 Day 113, current baseline safety assessments must be completed prior to Day 1 of Study AK002-003X. • Patients discontinued from treatment in Study AK002-003 due to high eosinophil counts prior to infusions 2, 3, or 4 may begin extended dosing within 6 months of last dose in Study AK002-003. Current baseline safety assessments must be completed prior to Day 1 of Study AK002-003X. • Patients will receive 26 monthly intravenous infusions of AK002 in an open-label manner. The first infusion of AK002 will be 1 mg/kg, and subsequent infusions will be 3 mg/kg. • If a monthly infusion of AK002 is missed, the patient will be permitted to make up the missed dose after the 26th month so that all patients have the chance to receive a total of 26 infusions.

Study Design cont.	• An EGD with biopsy will occur on Day 211 (±3), Day 547 (±3), and Day 729 (±3) or 28 (±3) days after last dose of study drug if early termination (ET) or if patient received additional missed doses. • Patients will be followed for 84 days after the last dose. Follow-up will occur on Extension Day 736 (±3), Day 757 (±3), and Day 785 (±3) or 35, 56, and 84 (±3) days after last dose of study drug if ET or if patient received additional missed doses. The extension study does not include fasting requirements. Patients underwent a standardized baseline evaluation of eating habits, food habits/restrictions, and food avoidance behaviors during Study AK002-003 and will be asked at study visits whether any changes have been made from the baseline diet. Total duration of Study AK002-003X will be approximately 28 months if doses are administered monthly and none are missed, or longer, as needed for the patient to receive all 26 doses.
Objective	The objective of the study is to generate open-label, longer-term safety, tolerability, and efficacy follow-up data in patients with EG and/or EoD who completed Study AK002-003 or were discontinued from treatment due to high eosinophil counts prior to infusions 2, 3, or 4. The objective of this extension study is also to give patients that received placebo in Study AK002-003 access to AK002.
Safety Endpoints	The safety and tolerability of AK002 will be assessed by determining the incidence, relationship to study drug, and severity of TEAE, withdrawals due to AE, vital signs, laboratory tests, changes in concomitant medication use due to AE, immunogenicity, and other safety parameters.
Pharmacodynamic/ Efficacy Endpoints	• Short-Form 36 Health Survey (SF-36) questionnaire • Gastrointestinal symptomatology (PRO questionnaire) • Change in blood eosinophil count • Change in eosinophil counts in gastric and/or duodenal biopsies
Study Population	Patients who complete Study AK002-003 or were discontinued from treatment due to high eosinophil counts prior to infusions 2, 3, or 4 will have the option to receive AK002 in an open-label manner. A patient was categorized as having completed Study AK002-003 if 4 infusions of study drug were administered and the patient was followed through Day 113 (±3) of Study AK002-003.

Patient Selection Criteria	**Inclusion Criteria** Patients are eligible for the study if all of the following criteria are met: 1) Provide written informed consent. 2) Completed Study AK002-003, defined as having received 4 infusions of study drug and followed through Day 113 (±3) in Study AK002-003 or discontinued from treatment due to high eosinophil counts prior to infusions 2, 3, or 4 and willing to begin extended dosing on or about Day 113 (for AK002-003 completers) or within 6 months of last dosing for patients discontinued from treatment. 3) If patient is on pre-existing dietary restrictions, willingness to note any changes that occur from the Baseline diet, throughout the study. 4) Able and willing to comply with all study procedures. 5) Female patients must be either post-menopausal for at least 1 year or surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months, or if of childbearing potential, have a negative pregnancy test and agree to use dual methods of contraception, or abstain from sexual activity until the end of the study, or for 120 days following the last dose of study drug, whichever is longer. 6) Male patients with female partners of childbearing potential must agree to use a highly effective method of contraception until the end of the study or for 120 days following the last dose of study drug, whichever is longer. 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 at any time during study participation.
	Exclusion Criteria Patients will be excluded from the study if they meet any of the following criteria: 1) Poor tolerance to previous administration of AK002 in the opinion of the Investigator. 2) Known hypersensitivity to any constituent of the study drug. 3) Any disease, condition (medical or surgical), or cardiac abnormality, which, in the opinion of the Investigator, would place the patient at increased risk. 4) Vaccination with live attenuated vaccines within 30 days prior to initiation of treatment in the study, during the treatment period, or vaccination expected within 5 half-lives (4 months) of study drug administration.

Patient Selection Criteria cont.	**Exclusion Criteria cont.** 4) cont. All types and formulations of vaccines (including live attenuated vaccines) authorized by FDA or other regulatory authority for the prevention of COVID-19 may be administered before, during, or after this study. The vaccine should not be administered within 7 days prior to and within 7 days after the administration of AK002 so that any side effects caused by either of the 2 medications can be more easily determined. 5) Women who are pregnant, breastfeeding, or planning to become pregnant while participating in the study. 6) Any other reason that, in the opinion of the Investigator or Medical Monitor, makes the patient unsuitable for enrollment. 7) Diagnosis of Hypereosinophilic Syndrome (HES), based on standard criteria (blood eosinophils >1500/µL with involvement of either the heart, nervous system, and/or bone marrow).
Test Product, Dose, and Administration	**AK002 Drug Product:** 10 mL supplied in 10R Type 1 clear glass vials for IV infusion with [redacted] pH 6.0, in water for injection (WFI). There is no placebo in this study. AK002 at a dose of 1 mg/kg will be prepared according to the patient's body weight and administered via infusion pump on Extension Day 1. Starting with the second infusion (Extension Day 29), the dose of AK002 will be increased to 3 mg/kg AK002, and 3 mg/kg will be administered for infusions 2 through 26. Patients will be observed for 1 hour after the end of dosing. Dosing will occur every 28 (±3) days for a total of 26 monthly doses. Dosing will occur on: Days 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, 533, 561, 589, 617, 645, 673, and 701 (±3 days). If a monthly infusion is delayed so that it occurs closer in the time frame to the next upcoming infusion, the late infusion will be considered skipped and may be made up after Day 701. Therefore, dosing could possibly occur on Day 729 (makeup for 1 skipped dose) and every 28 (±3) days after that, until 26 doses in total have been received. Prior to the first infusion of AK002, 60 mg oral prednisone will be given 12-24 hours prior to the infusion. The initial IV infusion should be given over at least a 4-hour period, and the second infusion should be given over at least a 3-hour period. Subsequent IV infusions (3–26) can be given over approximately 1 to 4 hours, depending on the patient's tolerance of the previous infusions and at the Investigator's discretion. Infusion rate schedules are described in more detail in the Pharmacy Manual.

Duration of Patient Participation	If no doses are considered skipped or missed, the total study duration for each patient will be approximately 28 months, which includes: • A treatment period of monthly AK002 infusions, administered every 28 (±3) days in an open-label manner for a maximum of 26 intravenous doses. • A post-treatment Follow-Up Period of 84 (±3) days following the last dose of AK002. If doses are considered skipped or missed, the total study duration will be extended beyond 28 months. The 84-day (±3) post-treatment Follow-Up Period still applies after the last dose of study drug.
Safety Evaluations	Safety and tolerability will be assessed throughout the study by monitoring and evaluating AE, including any complications resulting from the intravenous infusion. All AE will be collected from the start of study drug administration through 84 (±3) days after last dose of study drug. Severity of AE will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (or most current version). All AE will be assigned a severity grade and will be assessed to determine whether they are clinically significant and related to study drug. Additional safety evaluations include vital signs, CBC with differential, blood chemistry, urinalyses, symptomatic physical examinations, and ADA to AK002.
Pharmacodynamic/ Efficacy Evaluations	Patients will rate their quality of life using the non-disease-specific SF-36 at various study visits. Daily self-administration of a disease-specific patient questionnaire (PRO Questionnaire) will be used to evaluate signs and symptoms associated with EG and/or EoD. Patients with concomitant conditions of asthma, atopic dermatitis, and/or EoE will receive an additional question about each condition, as appropriate. Patients with EoE will also receive the daily Dysphagia Symptom Questionnaire (DSQ). Blood eosinophil counts will be assessed at each study visit.
Pharmacokinetic Evaluations	Blood (serum) will be collected for assessment of AK002 concentrations using a validated enzyme-linked immunosorbent assay method. Blood (serum) will be collected for assessment of AK002 ADA using a validated assay method. Pharmacokinetic blood samples will be obtained pre-dose on Extension Day 1 (obtained from Day 113 evaluations of Study AK002-003 or redrawn for patients that were discontinued from treatment in AK002-003), on Extension Day 561 (±3), and on Extension Day 736 (±3) or 35 (±3) days after last dose of study drug, if ET or if patient received additional missed doses.

Pharmacokinetic Evaluations cont.	ADA samples will be obtained predose on Extension Day 1, predose on all infusion days through Extension Day 365, Extension Day 533 (±3), and Extension Day 736 (±3) or 35 (±3) days after last dose of study drug, if ET or if patient received additional missed doses. In addition, ADA blood samples should be obtained at any time an immunogenicity-related AE occurs.
Statistical Analysis	Summary statistics will include the mean, median, standard deviation, minimum, and maximum for continuous variables and number and percentage of patients for categorical variables). No imputation will be used for missing data. Data will be analyzed as laid out in the Statistical Analysis Plan.
Rationale for Amendment 7	The following modifications were incorporated into Amendment 7: • Clarified that doses more than 15 days out of window will be considered skipped in order to standardize out-of-window deviations and get patients back on dosing track. • Clarified that any doses skipped or missed during the initial 701 days may be made up after Day 701 (26th dose) to give all patients a chance to receive a total of 26 doses. • Updated total duration of time to reflect the possibility of skipped/missed doses being made up after Day 701 and therefore extending the treatment period duration. • Changed Exclusion Criterion 4 to allow for COVID-19 vaccinations of any kind, including live, attenuated vaccines. • Updated total number of patients treated with AK002. • Clarified that male patients do not need to discontinue the study if their partner becomes pregnant, but the pregnancy must be followed to term. • Corrected Schedule of Assessments for Day 547 being an EGD day, not an infusion day. • Removed Baseline Diet compliance from histology Days 211 and 547. • Updated Appendix 19.8 to reflect that biopsy samples may be used for further research in the future.

2. Background

2.1 Siglec-8 and AK002

Siglec-8, a member of the CD33-related family of sialic acid-binding, immunoglobulin-like lectins (Siglecs), is a transmembrane cell surface protein with restricted tissue distribution, expressed selectively on the surface of mature eosinophils and mast cells, but not in early precursors of these cell populations. Siglec-8 contains 3 extracellular immunoglobulin-like domains, a transmembrane region, and a cytoplasmic tail containing 2 tyrosine-based signaling motifs including an immunoreceptor tyrosine-based inhibitory motif with inhibitory function. Engagement of Siglec-8 in mast cells can result in inhibition of mediator release, and in eosinophils, can induce apoptosis (Bochner, 2009). AK002 also shows potent antibody-dependent cellular cytotoxicity (ADCC) against eosinophils in vivo and in vitro.

2.2 Overview of Nonclinical Studies

AK002 is a humanized non-fucosylated immunoglobulin G1 (IgG1) monoclonal antibody directed against the inhibitory receptor Siglec-8, a member of the CD33-related family of Siglecs.

Siglec-8 has a restricted tissue distribution, expressed selectively on the surface of mature eosinophils and mast cells, but not in early precursors of these cell populations. In blood, binding of AK002 to Siglec-8 induces ADCC against eosinophils, leading to rapid and sustained depletion of these cells from circulation. In the tissue, AK002 induces direct apoptosis of eosinophils and inhibition of mast cells. This profile of activity may provide clinical benefit in diseases in which these cell types play a role, such as eosinophilic gastritis and eosinophilic duodenitis.

Siglec-8 is not expressed in species other than humans, and therefore 2 novel mouse models have been developed for in vivo testing of AK002. AK002 has been studied in Siglec-8 humanized and transgenic mouse models and with human blood and tissue cells. The first model uses immunodeficient mice capable of generating human immune cells including mast cells and eosinophils when engrafted with human hematopoietic stem cells. The ability of anti-Siglec-8 antibodies to inhibit mast cell-mediated reactions has been evaluated in this model. The second rodent model is a transgenic mouse line that expresses human Siglec-8. The expression of Siglec-8 on the cell surface in these mice is restricted to eosinophils, mast cells, and basophils, a pattern of surface expression equivalent to that in humans. Anti-Siglec-8 antibodies can prevent immunoglobulin E (IgE)-mediated anaphylaxis in this transgenic mouse line, indicating that Siglec-8 is pharmacologically active in the model. The ability of AK002 to affect mast cells and eosinophils has been evaluated in this model.

AK002 inhibits IgE-mediated mast cell degranulation and release of the newly formed mediator prostaglandin D2 in vitro without affecting mast cell viability. In peripheral blood preparations from normal human donors, AK002 shows selective depletion of eosinophils. Importantly, in a whole-blood cytokine-release assay using immobilized AK002 to enhance the potential for antibody crosslinking, AK002 did not lead to dose-dependent release of pro-inflammatory cytokines.

To evaluate the in vivo activity of anti-Siglec-8 antibodies in an immunocompetent rodent model, a transgenic mouse strain has been developed that selectively expresses human Siglec-8 on the surface of mouse mast cells, eosinophils, and basophils. In single- and repeat-dose studies in Siglec-8 transgenic mice, AK002 demonstrated selective depletion of peritoneal mast cells and circulating and tissue (spleen) eosinophils and basophils.

In 2 Good Laboratory Practice (GLP) toxicity and toxicokinetic studies, AK002 was well tolerated at doses of 50 mg/kg and 100 mg/kg, 5-fold and 10-fold, respectively, the level of the highest dose proposed to be studied in humans. AK002 showed sustained systemic exposure in Siglec-8 transgenic mice with an extended terminal half-life estimated as 272 hours or 337 hours following single intravenous administration of 50 mg/kg or 100 mg/kg, respectively, after 5 weekly doses at these dose levels. There was no evidence of anti-drug antibodies (ADA) in either study. Decreases in eosinophil counts in both sexes were observed, which reflect the expected pharmacology of AK002. The no-observed-adverse-effect-level following intravenous administration of AK002 to transgenic mice was 100 mg/kg, which supports the Phase 1 studies in humans.

2.3 Overview of Clinical Studies

AK002, administered as an intravenous infusion has been previously tested in healthy volunteers and in patients with indolent systemic mastocytosis (ISM), chronic urticaria (CU), severe allergic conjunctivitis (AC), mast cell gastritis, and eosinophilic gastritis (EG) and/or eosinophilic duodenitis (EoD), which was previously referred to as eosinophilic gastroenteritis (EGE) in previous versions of this protocol.

Multiple doses of 3 mg/kg AK002 have been given to patients with ISM, CU, severe AC, mast cell gastritis, and EG and/or EoD. In these studies, patients reported improvements in disease symptoms with AK002 pharmacodynamic (PD) activity being observed for prolonged periods of time and AK002 pharmacokinetic (PK) parameters demonstrating [redacted].

To date, over 300 healthy volunteers and patients with ISM, CU, severe AC, EG/EoD, EoE, and mast cell gastritis have been enrolled in clinical studies. In total, 65 EG/EoD patients were enrolled in the double-blind Study AK002-003 for which this protocol is the open-label extension.

In general, AK002 has been well tolerated. The most common treatment-emergent adverse events (TEAE) observed were infusion-related reactions (IRR). Most IRR were mild to moderate, and 2 IRR were classified as serious but resolved within 24 hours. Common symptoms of IRR were headache, nausea, sweating, flushing, and redness. Most IRR that occurred during the infusion could be managed by slowing or temporary interruption of the infusion, with minimal intervention. Transient lymphopenia was observed after infusion of AK002 but was not associated with any clinical consequence, and lymphocytes recovered within 24 hours. A sustained depletion of eosinophils was observed that is consistent with the mechanism of action of AK002. In 6 healthy volunteers who received 2 doses of 0.3 mg/kg, 4 weeks apart, the second dose was better tolerated than the first dose. This was also the case in patients with ISM, CU, severe AC, and EG/EoD, with fewer adverse events (AE) reported during the second and subsequent infusions when compared to the first infusion.

In the randomized, double-blind, placebo-controlled Phase 2 study of AK002 in 65 patients with EG and/or EoD, patients were randomized to receive monthly doses of placebo, low dose AK002 (0.3, 1, 1, and 1 mg/kg), or high dose AK002 (0.3, 1, 3, and 3 mg/kg) in a 1:1:1 ratio (Dellon, 2020). All primary and secondary endpoints were met in the study. There was a 97% and 92% mean reduction in eosinophils in the stomach/duodenum at the high dose and low dose, respectively, versus 10% increase on placebo ($p<0.0001$).

The reduction of eosinophils was associated with a statistically significant reduction in total symptom score (TSS) on 8 symptom intensity scores (TSS8) of 58% in the high dose group and 49% in the low dose group versus 24% reduction in the placebo group ($p=0.0012$ and $p=0.015$, respectively). Improvement in symptoms was observed within 24 hours of the first dose of study drug. In addition, 70% of high dose treated patients and 68% of low dose treated patients were treatment responders (defined as >30% improvement in TSS and >75% reduction from baseline in tissue eosinophils) versus 5% for placebo treated patients ($p<0.0001$).

When patients complete Study AK002-003 or are discontinued from treatment due to high eosinophil counts prior to infusions 2, 3, or 4, they are eligible to enter this open-label extension study, AK002-003X.

2.4 Eosinophilic Gastrointestinal Disorders

Eosinophilic gastrointestinal disorders (EGID) are chronic inflammatory disorders characterized by infiltration of eosinophils along different segments of the gastrointestinal tract, in the absence of any cause of the eosinophilia (Caldwell, 2014).

Eosinophilic gastritis and/or eosinophilic duodenitis represent what are believed to be rare types of EGID that are characterized by chronic, often severe inflammation due to patchy or diffuse infiltration of eosinophils into layers of the stomach, small intestine, or both (Prussin, 2014; Reed, 2015; Zhang, 2017).

The diagnosis is made based on clinical presentation (gastrointestinal symptoms) combined with increased tissue eosinophils in biopsy specimens from the stomach and/or small intestine without any other cause for the eosinophilia. Involvement of the small intestine is typically assessed by performing duodenal biopsies using an esophago-gastro-duodenoscopy (EGD) and has been referred to as EGE or eosinophilic enteritis, though EoD is more accurate.

The gastrointestinal symptoms are believed to be due to the release of inflammatory mediators from activated eosinophils, and likely mast cells. Symptoms that are often severe and debilitating commonly include abdominal pain, nausea, bloating, early satiety, loss of appetite, abdominal cramping, vomiting, diarrhea, and weight loss (Alhmoud, 2016; Lopez-Medina, 2015; Mansoor, 2017; Reed, 2015). Jensen (2016) estimated the prevalence of EG and EoD to be 6.3/100,000 and 8.4/100,000, respectively (for patients from 1 to 64 years of age). Mansoor (2017) estimated the overall prevalence of EG to be 5.1/100,000 persons.

Patients may also have concomitant atopic diseases like food allergy, asthma, and atopic dermatitis, which further impacts qualify of life and contributes to health care costs. Additionally, 8% to 10% of patients have concomitant EoE (Jensen, 2016).

There are no FDA-approved treatments for EG and/or EoD. Current therapies and disease management includes dietary restriction/elimination, proton pump inhibitors (PPI), antihistamines, systemic or swallowed corticosteroids, and occasional off-label use of immunomodulatory biologics (Prussin, 2014; Reed, 2015; Zhang, 2017).

Proton pump inhibitors have little to no benefit in patients with EG or EoD, despite reports of providing partial benefit in some patients with EoE (Katz, 2013). Restricted/elemental diets are not effective long-term treatment as they require strict compliance and, in the case of elemental diets, are expensive and often not reimbursed by insurance. In addition, compliance is very poor and patient quality of life is greatly impacted (Bedell, 2018; Peterson, 2013; Wechsler, 2014).

Corticosteroids, systemic or swallowed, have been shown to provide symptom relief but are not appropriate for long-term treatment due to numerous side effects and associated risks including adrenal insufficiency, bone demineralization, increased chance of infection, osteoporosis, behavioral issues, and weight gain.

By reducing the number of blood and tissue eosinophils and inhibiting the activation of mast cells, AK002 may be useful in the treatment of patients with EG and/or EoD. This premise is supported by the Phase 2 data with AK002 that shows significant improvements in histology and symptoms in these patients.

Given there are no approved therapies for these chronic and debilitating diseases, better treatment options are clearly needed to manage EG and EoD.

3. Rationale for Study and Dose Selection

Based on experience with AK002 in healthy volunteers and in patients with ISM, CU, severe AC, mast cell gastritis, and EG/EoD, the proposed AK002 dose regimen is up to 26 monthly intravenous infusions of AK002.

In the randomized, double-blind, placebo-controlled Phase 2 study of AK002 in 65 patients with EG and/or EoD, 2 dose levels were evaluated: a lower dose regimen (4 monthly doses of AK002 at 0.3, 1, 1, and 1 mg/kg) and a higher dose regimen (4 monthly doses of AK002 at 0.3, 1, 3, and 3 mg/kg). [redacted]

A starting dose of 1 mg/kg AK002 followed by a dose of 3 mg/kg AK002 for the subsequent infusions has been chosen for the Phase 2 extension study with AK002 in patients with EG and/or EoD.

4. Study Objective

The objective of the study is to generate open-label, longer-term safety, tolerability, and efficacy follow-up data in patients with EG and/or EoD who completed Study AK002-003 or were discontinued from treatment due to high eosinophil counts prior to infusions 2, 3, or 4.

The objective of this extension study is also to give patients that received placebo in Study AK002-003 access to AK002.

5. Study Design

5.1 Study Overview

This is a Phase 2, multicenter, open-label, extension study to evaluate the safety, tolerability, and efficacy of AK002 in patients with EG and/or EoD. Patients who complete Study AK002-003 will have the option to receive AK002 in an open-label manner. A patient will be categorized as having completed Study AK002-003 if 4 infusions of study drug are administered and the patient is followed through Day 113 (±3 days).

Patients who were discontinued from treatment in Study AK002-003 at the recommendation of the unblinded safety monitor for high eosinophil counts prior to infusions 2, 3, or 4, will have the option to receive AK002 in an open-label manner.

Patients who enroll in Study AK002-003X will receive monthly AK002 infusions for a maximum of 26 intravenous doses. During Extension Study AK002-003X, patients will maintain the same patient number that was assigned in Study AK002-003.

Safety will be assessed by body weight, vital signs, symptom-directed physical examination, complete blood count (CBC) with differential, blood chemistry, urinalysis, and assessment of AE (including adverse events of special interest [AESI] and serious adverse events [SAE]). In addition, blood samples will be obtained for evaluation of anti-drug antibodies (ADA).

This extension study does not include fasting requirements. Patients underwent a standardized baseline evaluation of eating habits, food habits/restrictions, and food avoidance behaviors during Study AK002-003 and will be asked at study visits whether any changes have been made from the baseline diet.

Patients completing Study AK002-003 and wanting to enter the extension study will begin extended dosing on or about Day 113 of Study AK002-003 (following final assessments of Study AK002-003), which will be considered Day 1 of Study AK002-003X. If patients cannot start extended dosing within 45 days of AK002-003 Day 113, current baseline safety assessments must be completed prior to Day 1 of Study AK002-003X. Patients discontinued from treatment in Study AK002-003 due to high eosinophil counts prior to infusions 2, 3, or 4 may begin extended dosing within 6 months of the last dose in Study AK002-003.

Patients discontinued from the AK002-003 study for high eosinophil counts and patients that completed AK002-003 but were not enrolled into AK002-003X within 45 days of Day 113 will require current safety evaluations.

Patients will receive up to 26 monthly intravenous infusions of AK002 in an open-label manner. The first infusion of AK002 will be 1 mg/kg, and subsequent infusions will be 3 mg/kg.

If a monthly infusion of AK002 is missed the patient will be permitted to make up the missed dose after the 26th month so that all patients have the chance to receive a total of 26 infusions.

An EGD with biopsy will occur on Day 211 (±3), Day 547 (±3), and Day 729 (±3) or 28 (±3) days after the last dose of study drug, if early termination (ET) or if patient received additional missed doses.

Patients will be followed for 84 (±3) days after the last dose of study drug. Follow-up visits will occur on Extension Day 736 (±3), Day 757 (±3), and Day 785 (±3) or 35 (±3), 56 (±3), and 84 (±3) days after last dose of study drug, if ET or if patient received additional missed doses.

Total duration of Study AK002-003X will be approximately 28 months if doses are administered monthly and none are missed, or longer, as needed for the patient to receive all 26 doses.

Approximately 60 patients will be enrolled in Study AK002-003X, based on enrollment of Study AK002-003.

5.2 Schedule of Events

The overall schedule of procedures and assessments is shown in Table 1.

Table 1 Study AK002-003X Schedule of Assessments

Assessment Description	Prior to Dose 1	Treatment Period (25 months or longer if any monthly doses have been missed/skipped)[30]								Follow-Up Period (12 weeks)			
		Dose # 1 Day 1	Dose # 2 Day 29 (±3)	Doses #3–8 Day 57–197[26] (±3)	Day 211 (±3)	Doses #9–20 Day 225–533[27] (±3)	Day 547 (±3)	Doses #21–26 Day 561–701[28] (±3)	Additional Infusion Day(s) *only* if previous infusions have been missed[29]	Day 729[1] (±3) or 28 days after last dose	Day 736[1] (±3) or 35 days after last dose	Day 757[1] (±3) or 56 days after last dose	Day 785[1] (±3) or 84 days after last dose
Informed consent	X												
Prior/Concomitant Medications[2]		X	X	X	X	X	X	X	X	X	X	X	X
Body weight[3]		X[4] (predose)	X (predose)	X (predose)		X (predose)		X (predose)	X (predose)		X	X	X
Vital Signs[5]		X[4]	X	X		X		X	X		X	X	X
SF-36 Health Survey		X[4]	X	X		X		X	X		X	X	X
ePRO Activation and Training[6]	X												
ePRO Questionnaire (may include Additional Questions)[7]		<---------- Complete electronically one time daily ---------->											
PGIC Questionnaire[13]			X	X									
Baseline Diet Changes		X[4]	X	X		X		X	X		X	X	X
Urine Dipstick Pregnancy Test[8]		X[4]	X	X		X		X	X		X		
Eligibility Assessment	X												
Current Safety Evaluations, as needed[9]	X												
Access IRT to enter PID and current body weight[10]		X	X	X		X		X	X				
Premedication: Prednisone[11]	X												
Study Drug Administration[12]		X	X	X		X		X	X				
Symptom directed Physical Exam[14]		X[4]	X	X		X		X	X		X	X	X
Blood for Hematology with differential[15, 16]		X[4]	X	X		X		X	X		X	X	X
Blood for Chemistry[15, 17]		X[4]	X	X		X		X	X		X	X	X
Urinalysis[15, 18]		X[4]									X		
Blood for PK[15, 19]		X[4]									X		

Table 1 Study AK002-003X Schedule of Assessments

Assessment Description	Prior to Dose 1	Treatment Period (25 months or longer if any monthly doses have been missed/skipped)[30]								Follow-Up Period (12 weeks)			
		Dose # 1 Day 1	Dose # 2 Day 29 (±3)	Doses #3–8 Day 57–197[26] (±3)	Day 211 (±3)	Doses #9–20 Day 225–533[27] (±3)	Day 547 (±3)	Doses #21–26 Day 561–701[28] (±3)	Additional Infusion Day(s) *only* if previous infusions have been missed[29]	Day 729[1] (±3) or 28 days after last dose	Day 736[1] (±3) or 35 days after last dose	Day 757[1] (±3) or 56 days after last dose	Day 785[1] (±3) or 84 days after last dose
Blood for ADA[15, 20]		X	X	X		X[20]					X		
EGD with Biopsy[21, 22]					X		X			X			
Non-serious adverse events[23]		X	X	X	X	X	X	X	X	X	X	X	X
Adverse events of special interest[24]		X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events[25]		X	X	X	X	X	X	X	X	X	X	X	X

Table 1 Notes

ADA: Anti-Drug-Antibody
EGD: Esophago-Gastro-Duodenoscopy
Eos: Eosinophil
ET: Early termination
Ext: Extension
IRT: Interactive response technology
IV: Intravenous
PGIC: Patient Global Impression of Change
PID: Patient identification number
PK: Pharmacokinetic
PRO: Electronic Patient Reported Outcome (questionnaire)

1) The ET visits should be conducted 28 (±3), 35 (±3), 56 (±3) and 84 (±3) days after the last dose of study drug or prior to this, if necessary, to ensure compliance with the visit. If only one ET visit is possible, EGD and end-of-study procedures (Day 35 after last dose of study drug) may occur on the same day. If the end-of-study visit occurs more than 35 days after the last dose of study drug, then perform the visit as soon as possible. In this case, the procedures listed under the 28-day post and 35-day post study drug visit will be conducted unless otherwise directed by the Medical Monitor.

2) All concomitant medications taken within 30 days of enrolling into AK002-003X will be captured. All medications used during the study for the treatment of infusion related reactions, adverse events, or for the conduct of EGD will be captured.

3) Body weight (in kg) will be recorded on all infusion days and on follow-up Days 736, 757, and Day 785 or 35, 56, and 84 days after last dose, if ET or if previous missed infusions were made up. Current body weight, or body weight from 1 day prior will be used to calculate the amount of AK002 to be mixed with NaCl for the appropriate dose to be administered on each infusion day.

4) Do not collect if procedure was performed ≤45 days prior to Extension Day 1 (as part of the Day 113 assessment for Study AK002-003). Differential cell counts collected on Day 113 for Study AK002-003 will not be unblinded.

5) Vital signs including systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate will be taken after the patient has been at rest for ≥5 minutes and before any blood draw. Vital signs will be measured on all dosing days pre-dose, 15 minutes (±5 minutes) after the start of infusion, and immediately following the end of infusion (15 ±5 minutes).

6) Activate PRO questionnaire and provide patient with unique username and password. PRO questionnaire should be activated for all patients on Extension Day 1. Patients with concomitant history of asthma, atopic dermatitis, or EoE will receive an extra question, about each, as appropriate.

Table 1 Notes cont.

7) The EG/EoD PRO should be completed around the same time of the day. All patients receive the 10-question EG/EoD questionnaire. Only patients with concomitant conditions of asthma, atopic dermatitis, and/or EoE will receive an additional question for each condition, as appropriate. Patients with concomitant EoE will also receive the once-daily DSQ.

8) Urine for Dipstick Pregnancy test will be collected predose for patients of childbearing potential on all infusion days and on Day 736 (or Day 35 after last dose of study drug, if ET or if previous missed infusions were made up). Test kits will be supplied by the central laboratory. Tests will be completed on site and evaluated prior to infusion(s).

9) Blood for Safety Evaluations (chemistry, hematology with differential, and urinalysis) to be collected if Extension Day 1 is >45 days from AK002-003 Day 113 or if patient was withdrawn from AK002-003 due to high eosinophil counts. Hematology and chemistry results must be available prior to randomization. If patient is suspected of exposure to helminthic parasites, stool sample should also be collected.

10) Cenduit IRT to be used for investigational product dispensation on all infusion days.

11) All patients will take 60 mg oral prednisone 12–24 hours prior to the first infusion. An approved alternative(s) may be used with the approval of the Medical Monitor. Premedication may be administered prior to subsequent infusions at the Investigator's discretion, but only with written approval from the Medical Monitor. If a patient is significantly outside their 28-day treatment window, a hematology test will be collected and the eosinophils evaluated. If the eosinophils are no longer suppressed, the patient will be given premedication of 60 mg prednisone, and the infusion may be completed using a slower infusion rate.

12) Study drug will be administered as a single peripheral intravenous infusion over at least 4 hours on Extension Day 1, over at least 3 hours on Extension Day 29, and over 1 to 4 hours thereafter, depending on prior tolerance to study drug infusion. Please refer to the Pharmacy Manual for detailed instructions on study drug preparation, administration, and infusion rates. Infusion must be completed within 8 hours of preparation of study drug.

13) Patient Global Impression of Change (PGIC) questionnaire (Appendix 19.6) will be completed by the patient on Extension Day 29 (±3), Day 57 (±3), and Day 85 (±3).

14) A symptom-directed physical examination (including assessment of possible infusion site reactions) will be performed by the Investigator or designee, as needed, if any symptoms are reported.

15) Specimen processed by central laboratory. See central laboratory manual for collection and processing details.

16) Blood for CBC with differential, including absolute blood eosinophil and basophil counts, will be obtained just prior to each infusion and 1 hour after the end of each infusion, as well as on Extension Days 736, 757, and 785 (±3 days) or 35, 56, and 84 (±3 days) after last dose of study drug, if ET or if previous missed infusions were made up.

17) Blood for Chemistry will be obtained just prior to each infusion, as well as on Extension Days 736, 757, and 785 (±3 days) or 35, 56, and 84 (±3 days) after last dose of study drug, if ET or if previous missed infusions were made up.

18) Urine for Urinalysis will be collected on Extension Day 1 and Extension Day 736 (±3) or 35 (±3 days) after last dose of study drug, if ET or if previous missed infusions were made up.

19) Blood for PK will be collected on Extension Day 1 and Extension Day 736 (±3) or 35 (±3 days) after last dose of study drug, if ET or if previous missed infusions were made up.

20) Blood samples for ADA will be collected predose on all dosing days through Extension Day 365, on Extension Day 533 (±3), and Extension Day 736 (±3) or 35 (±3) days after last dose of study drug, if ET or if previous missed infusions were made up. ADA will also be collected when an immunogenicity-related adverse event occurs.

21) Specimen processed by Surgical Pathologist of Dallas, via the Central Lab. See Histology Manual for processing directions.

22) See Appendix 19.8 for biopsy assessments. EGD should occur on Day 211 (±3), Day 547 (±3) and Day 729 (±3) or 28 (±3) days after the last dose of study drug if the patient discontinues the study early or if previous missed infusions were made up, and patient agrees to have an early-termination biopsy.

23) Non-serious adverse events will be captured from Day 1 (first dose of study drug) through Day 785 or 84 days after last dose of study drug, if ET or if previous missed infusions were made up.

Table 1 Notes cont.

24) Adverse events of special interest will be captured from Day 1 (first dose of study drug) through Day 785 or 84 days after last dose of study drug, if ET or if previous missed infusions were made up.

25) Serious adverse events of special interest will be captured from Day 1 (first dose of study drug) through Day 785 or 84 days after last dose of study drug, if ET or if previous missed infusions were made up.

26) Monthly doses # 3–8 will occur on Days 57, 85, 113, 141, 169, and 197 (±3 days).

27) Monthly doses # 9–20 will occur on Days 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, and 533 (±3 days).

28) Monthly doses # 21–26 will occur on Days 561, 589, 617, 645, 673, and 701 (±3 days).

29) ***Only if previous infusions have been missed***, make-up dosing may occur on Day 701 + 28 days (±3), until 26 total doses have been administered.

30) Doses will be considered missed if they occur more than 15 days outside the protocol-specified window.

6. Criteria for Evaluation

6.1 Safety Endpoints

The safety and tolerability of AK002 will be assessed by determining the following:

- Symptom-directed physical examination (Section 11.3.3)
- Changes in body weight (Section 11.3.2) and vital signs (Section 11.3.4)
- Hematology (Section 11.2.4)
- Changes in concomitant medication use due to AE (Section 11.3.1)
- Blood chemistry (Section 11.4.2)
- Urinalysis (Section 11.4.4)
- ADA (Section 11.4.5)
- Adverse events (Section 13.)

6.2 Pharmacokinetic Endpoints

Blood (serum) will be collected for assessment of AK002 concentrations using a validated enzyme-linked immunosorbent assay method. Blood (serum) will be collected for assessment of ADA to AK002 using a validated assay method.

Pharmacokinetic blood samples will be obtained predose on Extension Day 1 (obtained from Day 113 evaluations of Study AK002-003 or redrawn for patients that were discontinued from treatment in AK002-003) and on Extension Day 561 (±3) and Extension Day 736 (±3) or 35 (±3) days after last dose of study drug, if ET or if patient received additional missed doses.

ADA samples will be obtained predose on Extension Day 1, predose on all infusion days through Extension Day 365, on Extension Day 533 (±3), and on Extension Day 736 (±3) or 35 (±3) days after last dose of study drug, if ET or if patient received additional missed doses.

6.3 Efficacy Endpoints

Daily self-administration of a disease-specific patient questionnaire (PRO Questionnaire) will be used to evaluate signs and symptoms associated with EG and/or EoD. Changes in quality of life will be measured by the Short-Form 36 Health Survey (SF-36) questionnaire. Changes in the number of eosinophils in gastric and/or duodenal mucosa from baseline will also be evaluated.

6.4 Pharmacodynamic Endpoints

Change in blood eosinophils will be assessed at study visits.

7. Patient Selection

7.1 Number of Patients

Approximately 60 patients will be enrolled in Study AK002-003X.

7.2 .Study Population

Patients who complete Study AK002-003 or were discontinued from treatment in Study AK002-003 study for high eosinophil counts prior to infusions 2, 3, or 4 and meet the inclusion criteria in Section 7.3 and exclusion criteria in Section 7.4 will have the option to receive AK002 in an open-label manner. A patient is categorized as having completed Study AK002-003 if 4 infusions of study drug were administered and the patient was followed through Day 113 (±3) of Study AK002-003.

7.3 Inclusion Criteria

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

1) Provide written informed consent.

2) Completed Study AK002-003, defined as having received 4 infusions of study drug and followed through Day 113 (±3) in Study AK002-003 or discontinued from treatment due to high eosinophil counts prior to infusions 2, 3, or 4, and willing to begin extended dosing on or about Day 113 (for AK002-003 completers) or within 6 months of last dosing for patients discontinued from treatment.

3) If patient is on pre-existing dietary restrictions, willingness to note any changes that occur from the Baseline diet, throughout the study.

4) Able and willing to comply with all study procedures.

5) Female patients must be either post-menopausal for at least 1 year or surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months, or if of childbearing potential, have a negative pregnancy test and agree to use dual methods of contraception, or abstain from sexual activity until the end of the study, or for 120 days following the last dose of study drug, whichever is longer.

6) Male patients with female partners of childbearing potential must agree to use a highly effective method of contraception until the end of the study or for 120 days following the last dose of study drug, whichever is longer. 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 at any time during study participation.

7.4 Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

1) Poor tolerance to previous administration of AK002 in the opinion of the Investigator.
2) Known hypersensitivity to any constituent of the study drug.
3) Any disease, condition (medical or surgical), or cardiac abnormality, which, in the opinion of the Investigator, would place the patient at increased risk.
4) Vaccination with live attenuated vaccines within 30 days prior to initiation of treatment in the study, during the treatment period, or vaccination expected within 5 half-lives (4 months) of study drug administration. All types and formulations of vaccines (including live attenuated vaccines) authorized by FDA or other regulatory authority for the prevention of COVID-19 may be administered before, during, or after this study. The vaccine should not be administered within 7 days prior to and within 7 days after the administration of AK002 so that any side effects caused by either of the 2 medications can be more easily determined.
5) Women who are pregnant, breastfeeding, or planning to become pregnant while participating in the study.
6) Any other reason that, in the opinion of the Investigator or Medical Monitor, makes the patient unsuitable for enrollment.
7) Diagnosis of Hypereosinophilic Syndrome (HES) based on standard criteria (blood eosinophils >1500/μL with involvement of either the heart, nervous system, and/or bone marrow).

8. Concurrent Medications

Concomitant medications include both prescribed and over-the-counter medications and will be recorded in the electronic Case Report Forms (eCRF).

Any medication must have been stopped as required in AK002-003 exclusion criteria. 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. Immediately prior to the first infusion, the study site personnel should ensure that the patient continues to meet the inclusion criteria and none of the exclusion criteria (including no receipt or use of prohibited medications).

All medications taken during participation in this study must be documented on the eCRF. All medications used to treat IRR or AE must also be documented.

8.1 Prohibited Medications

Any medications that may interfere with the study such as immunosuppressive or immunomodulatory drugs (including azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, tacrolimus, anti-tumor necrosis factor, anti-interleukin-5, anti-interleukin-5 receptor, dupilumab, anti-IgE antibodies, omalizumab) or systemic or topical corticosteroids with a dose >10 mg/day of prednisone or equivalent.

There may be special circumstances where the use of some of these medications may be acceptable. In these cases, approval must be obtained from the Allakos Medical Monitor.

Vaccination with live attenuated vaccines within 30 days prior to initiation of treatment in the protocol, during the treatment period, or vaccination expected within 5 half-lives (4 months) of AK002 administration is prohibited.

All types and formulations of vaccines (including live attenuated vaccines) authorized by FDA or other regulatory authority for the prevention of COVID-19 may be administered before, during or after this study. The vaccine should not be administered with 7 days prior to and within 7 days after the administration of AK002 so that any side effects caused by either of the 2 medications can be more easily determined.

8.2 Allowed Medications

Medications, other than those that are prohibited (Section 8.1), such as antihistamines, leukotriene antagonist, corticosteroids with a daily dose ≤10 mg/day of prednisone and mast cell stabilizers are allowed during the study and, unless required due to unforeseen medical necessity, doses are to remain stable.

All medication use will be documented in the eCRF.

9. Study Treatment

9.1 Formulation of Test Product

AK002 is a humanized non-fucosylated IgG1 monoclonal antibody directed against Siglec-8. AK002 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°–8°C. The AK002 formulation is [redacted] pH 6.0, in sterile water for injection.

Note: AK002 will be referred to as "study drug." There is no placebo in the extension study.

9.2 Study Drug Packaging and Labeling

AK002 drug product is supplied as a sterile liquid in a single-use 10R glass vial with a fill volume of approximately 10.6 mL. Each vial will be labeled with the required investigational use statement, lot number, Sponsor name, and directions for storage. Each vial will also contain a tear-off label with lot and/or kit number and space to document patient identification (PID) number and preparation date. This tear-off label should be applied to the Investigational Product Dose Calculation and Preparation Worksheet and maintained with the source documents.

Glass vials are plugged with Teflon-coated rubber stoppers and sealed with aluminum seals.

9.3 Supply of Study Drug to the Investigational Site

The Sponsor (or designee) will ship study drug to the investigational sites. The initial study drug shipment will be shipped after all required regulatory documentation and approvals have been received by the Sponsor, and contract has been executed. Subsequent study drug shipments will be triggered automatically based on predetermined supply levels and enrollment activity at the site.

9.4 Study Drug Dosage/Dosage Regimen

The first infusion of AK002 will be 1 mg/kg. Starting with the second infusion (Extension Day 29), the dose of AK002 will be increased to 3 mg/kg, and 3 mg/kg will be administered for all subsequent infusions.

Dosing will occur on Extension Days 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, 533, 561, 589, 617, 645, 673, and 701 (±3 days).

If a monthly infusion is delayed so that it occurs closer in the time frame to the next upcoming infusion, the late infusion will be considered skipped and may be made up after Day 701. Therefore, dosing could possibly occur on Day 729 (makeup for 1 skipped dose) and every 28 (±3) days after that, until 26 doses in total have been received.

The exact dose will be calculated prior to each infusion and based on current patient body weight. Study drug will be administered as a single peripheral intravenous infusion using an infusion pump as indicated in the study Pharmacy Manual at the study visits specified in Table 1.

9.5 Preparation of Study Drug

A study pharmacist or designee will prepare the study drug for each infusion. Based on patient body weight obtained the day of or the day prior to dosing, the designated study pharmacist will prepare the appropriate dilution of AK002 for intravenous administration.

Appropriate aseptic technique will be used, and the drug will be prepared according to the pharmacy manual for AK002. Please refer to the Pharmacy Manual for additional details and step-by-step instructions regarding study drug preparation.

The infusion must be completed within 8 hours of preparation. Preparation is when the AK002 is first mixed with the NaCl.

Based on current USP 2019 guidelines, AK002 is not considered to be a hazardous drug, and therefore, special precautions do not need to be taken when handling or preparing the study drug.

9.6 Study Drug Administration

Specific instructions on administration and supplies required for administration are detailed in the Pharmacy Manual. In general, study drug will be infused through a peripheral vein intravenous set. The intravenous line may be kept open before and after the infusion with sufficient quantities of 0.9% NaCl to assure patency, as needed.

A volume of 100 mL* of the calculated dose of study drug will be infused over at least 4 hours on Extension Day 1, over at least 3 hours on Extension Day 29, and over 1 to 4 hours thereafter, depending on the patient's tolerance of the previous infusions and at the Investigator's discretion. If the infusion is slowed or interrupted, the time may be extended longer than 4 hours, as long as it does not exceed 8 hours.

* Due to the rounding of the total infusion volume by some programmable infusion pumps, an infusion of 99 to 101 mL will be considered a complete infusion and will not be recorded as a deviation of the study.

Prior to first infusion of AK002, patients will be premedicated with 60 mg oral prednisone (or approved equivalent) 12–24 hours prior to the start of the study drug infusion. For subsequent infusions, premedication may be used at the discretion of the Investigator, for patient tolerability, and with approval from the Medical Monitor. An alternate premedication regimen may be used with the approval of the Medical Monitor.

The intravenous infusion may be interrupted and/or the rate may be reduced if a patient has an IRR. The time that the infusion is initiated/concluded (including any interruptions) will be documented in the eCRF. If the infusion is restarted after an interruption, the infusion must be completed within 8 hours of preparation. Administration will be discontinued if, in the opinion of the Investigator, an interrupted infusion cannot be restarted for safety reasons or if the infusion cannot be completed within 8 hours of preparation. Administration will also be discontinued in any patient experiencing a serious adverse event during the course of the infusion.

The patient will be observed for 4 hours after the end of the first infusion and if no issues are noted, will be observed for at least 1 hour for subsequent infusions, as per Investigator discretion and depending on tolerance to prior infusions.

9.7 Study Drug Storage

AK002 will be stored by the study sites at 2°–8°C under lock at the designated pharmacy. Access will be restricted to designated pharmacy staff. The 0.9% NaCl will be stored at ambient temperature, per manufacturer's requirements. All study drug will be stored in an area that is 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 captured as a deviation. The Sponsor will notify the site if the study drug is to be quarantined or can be used.

9.8 Study Drug Accountability

The site's study pharmacist/designee is responsible for maintaining accurate and current records accounting for the receipt, dispensing, preparation, use, return (or destruction), and final disposition of all investigational product. All dosage calculations will be documented on the source documents. The Master Investigational Product Accountability Log, or similar should be used to capture receipt, dispensing, and return (or destruction). Electronic investigational product accountability systems may be used, depending on site preference, as long as the same information is captured. The study monitor will verify entries on these documents throughout the course of the study.

Study drug may or may not be labeled with kit numbers.

10. Patient Numbering, Stratification, Randomization, and Blinding

10.1 Patient Numbering

Each patient who provides informed consent will be identified by the PID assigned in Study AK002-003. The patient will maintain the same PID throughout the entire study. Patients will maintain the same PID when entering AK002-003X.

A patient is considered enrolled in the AK002-003X study when the subject receives the first dose of open-label AK002.

10.2 Stratification and Randomization

There will be no randomization as all patients will receive AK002.

10.3 Blinding

There will be no blinding as all patients will receive AK002.

11. Study Procedures and Guidelines

Table 1 provides the schedule of assessments to be performed for the duration of the study. When multiple evaluations are scheduled at the same time point, the priority for each will be as follows:

- SF-36 (self-administered format) should be completed at the beginning of the study visit before any other assessments or procedures.
- PRO Questionnaire should be completed by each study subject daily (at approximately the same time each day) during the treatment and follow-up periods.
- Vital signs will be obtained after the patient has been at rest for ≥5 minutes.
- Symptom-directed physical examinations can be performed, and urine samples can be collected either before or after other evaluations.

11.1 Dietary and Lifestyle Restrictions

This extension study does not include fasting requirements. Patients underwent a standardized baseline evaluation of eating habits, food habits/restrictions, and food avoidance behaviors during Study AK002-003 and will be asked at AK002-003X study visits if any changes have been made to the baseline diet since the previous study visit.

11.2 Pharmacodynamic/Efficacy-Related Procedures

11.2.1 Efficacy-Related: Short Form-36 Health Survey

A paper version of the SF-36 (Appendix 19.1) will be completed by the patient as part of the Day 113 visit of Study AK002-003 and will serve as the baseline assessment. Starting on Extension Day 29, an electronic version of the SF-36 will be completed at select study visits during the Extension Study. A paper version of the SF-36 is available to patients in case they are not able to complete the electronic version.

11.2.2 Efficacy-Related: PRO Questionnaire

An electronic version of the PRO questionnaire (Appendix 19.2) will be completed daily at approximately the same time by the patient throughout the study.

The recall period for each PRO entry is approximately 24 hours. Patients will not be able to complete a questionnaire more than 24 hours after it is due and will not be able to go back and make any corrections or changes to the data originally entered. This information will be automatically captured and maintained in the ePRO system of the EDC.

A paper version of the PRO questionnaire is available to subjects in case they are not able to complete the electronic version. Only one PRO should be completed per day, and the recall period should not be any more than approximately 24 hours long.

If patients have a history of concomitant atopic dermatitis, atopic asthma, or EoE, an extra question (per condition) will be populated on the PRO website for the patients to complete daily. A paper version of these questions is available, should the website not be accessible (Appendix 19.6). Additionally, for patients with a history of EoE, the DSQ (Appendix 19.7) will be administered daily. The DSQ consists of 4 questions that will be populated on the ePRO website.

11.2.3 Patient Global Impression of Change (PGIC)

A paper PGIC questionnaire (Appendix 19.6) will be completed at the times identified in Table 1.

11.2.4 Pharmacodynamic: Complete Blood Count with Differential

Blood will be obtained for CBC with differential at visits and times identified in Table 1. The differential cell count on Day 113 of Study AK002-003 will remain blinded.

The blood sample will be processed and shipped in accordance with laboratory manual and laboratory kit instructions. A central laboratory will analyze the blood sample and provide results for CBC with differential, including hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell count, and absolute differential count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils).

11.2.5 Esophago-Gastro-Duodenoscopy with Biopsy

An EGD with biopsy will be performed on Day 211 (±3), Day 547 (±3), and Day 729 (±3) or 28 (±3) days after last dose of study drug, if ET. Biopsy samples will be collected according to standardized instructions and will be sent to the Central Lab designee for fixing and staining. A Central reader will report, among other things, maximum number of eosinophils per hpf, maximum number of tryptase-positive mast cells per hpf, and gastric biopsies will be graded using the Sydney System on inflammation, metaplasia, atrophy, and reactive gastropathy. The Marsh Scale Classification will be used to grade duodenal samples. The baseline EGD from Study AK002-003 will be used for comparison.

11.3 Safety-Related Procedures

11.3.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at each study visit, if changes are made. Dose, route, unit, frequency of administration, indication for administration, and dates of medication will be captured. Record any medication received during the study through Extension Day 785 or 84 days after last dose of study drug if ET, or if previous missed infusions were made up.

11.3.2 Body Weight

Weight will be measured pre-dose and used to determine the amount of study drug to be mixed with NaCl for infusion. Body weight will be entered into the interactive response technology system (IRT) for each dosing visit and will also be recorded on the Investigational Product Dose Calculation and Preparation Worksheet that the pharmacist will maintain and document for each patient's dose calculations. Body weight should be collected on the day of each study drug infusion, or the day prior to each infusion. Body weight will be captured through Extension Day 785 or 84 days after last dose of study drug if ET, or if previous missed infusions were made up.

11.3.3 Symptom-Directed Physical Examination

A symptom-directed physical examination, an examination of reported or observed patient symptoms warranting examination (in the opinion of the Investigator) including assessments of possible infusion site reactions and IRR, will be performed by either the Investigator or a qualified designee at certain study visits through Extension Day 785 or 84 days after last dose of study drug if ET, or if previous missed infusions were made up. New, abnormal, and clinically significant physical examination findings must be documented and will be followed by the study doctor or Subinvestigator at the next scheduled visit or sooner if clinically indicated or referred to a non-study physician.

11.3.4 Vital Signs

Vital signs, including systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate, will be taken after the patient has been at rest for ≥5 minutes and before any blood draw (except post-infusion for which vital signs will be obtained as described below).

On dosing days, vital signs will be measured pre-dose, 15 (±5) minutes after the start of infusion, and immediately following the end of infusion (+5 minutes). Please refer to the schedule of assessments in Table 1.

11.4 Clinical Laboratory Measurements

Blood and urine samples for clinical safety laboratory tests will be collected at the time points presented in Table 1. Investigators may have additional laboratory tests performed for the purpose of planning treatment administration or following AE or abnormal laboratory values.

The site will process and ship blood and urine samples per central laboratory instructions. A central laboratory or designee will analyze blood and urine samples and provide results for the following clinical safety laboratory tests: CBC (Section 11.2.4), blood chemistry (Section 11.4.2), urine pregnancy test (Section 11.4.3), and urinalysis (Section 11.4.4).

Clinical laboratory testing may be performed locally due to issues associated with the COVID-19 pandemic, with prior approval from Allakos. The site will strive to use the central lab whenever possible.

For any laboratory test value outside the reference range, the Investigator will determine clinical significance (Not Clinically Significant [NCS] or Clinically Significant [CS]). An abnormal lab value should be deemed CS if any of the following conditions are met:

- The abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline.
- The abnormality is of a degree that requires additional active management, e.g., change of study drug dose, discontinuation of the study drug, close observation, more frequent follow-up assessments, or further diagnostic investigation.

Therefore, a clinically significant lab value is one that indicates a new disease process, an exacerbation or worsening of an existing condition, or requires further action to be taken.

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.
- Record as an adverse event any laboratory test value after start of study drug that:
  - The Investigator considers clinically significant
  - Requires a patient to be discontinued from the study, or
  - Requires a patient to receive treatment.

11.4.1 Complete Blood Count with Differential

Blood will be obtained for CBC with differential as described in Section 11.2.4.

11.4.2 Blood Chemistry Profile

Blood for chemistry tests will be processed and shipped in accordance with central laboratory manual and laboratory kit instructions. A central laboratory will analyze the serum sample and provide results for chemistry tests including sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, creatine kinase, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, and lactate dehydrogenase.

An aliquot of blood chemistry will be processed and shipped frozen in accordance with the laboratory manual and laboratory kit instructions.

11.4.3 Pregnancy Test

Women of childbearing ability will provide a urine sample for on-site pregnancy (human chorionic gonadotropin) testing. The site will perform the urine pregnancy test using an indicator stick from the pregnancy test kit supplied by the central laboratory. This test will be assessed prior to the start of each study drug infusion. A pregnancy test will also be performed on Extension Day 736 or 35 (±3) days after last dose, if ET or if previous missed infusions were made up.

For the purposes of the study, patients with FSH levels ≤30 mIU/mL should receive pregnancy testing.

11.4.4 Urinalysis

Urine samples will be processed and shipped in accordance with the laboratory manual and laboratory kit instructions. A central laboratory will analyze the urine sample for specific gravity, pH, protein, glucose, ketones, blood, and leukocyte esterase.

11.4.5 Anti-Drug Antibodies

Serum samples for ADA determination will be processed and shipped frozen in accordance with the laboratory manual and laboratory kit instructions. A central laboratory will analyze the sample for ADA using a validated assay method. Blood samples for ADA will also be collected anytime an immunogenicity-related AE occurs.

11.4.6 Blood for Pharmacokinetics and Storage

Blood samples for serum pharmacokinetic assessments will be processed and shipped frozen in accordance with the study laboratory manual and laboratory kit instructions.

AK002 concentrations will be determined by the central laboratory or designee using a validated enzyme-linked immunosorbent assay method. Specific information on pharmacokinetic sample collection, processing, storage, and shipment will be provided in the central laboratory manual.

11.4.7 Current Safety Evaluations (if needed)

Current safety evaluations are required for patients that were previously withdrawn from AK002-003 or whose Day 113 visit in AK002-003 is >45 days before Extension Day 1 in AK002-003X.

Central lab samples may be collected and processed as per instructions in the Central Lab Manual or Local Lab samples may be used, as long as results are available for review prior to enrollment (first dose in AK002-003X). Blood chemistry, CBC with differential (including absolute eosinophil count), and urinalysis must be reviewed.

The Investigator may choose to conduct other safety procedures prior to enrolling the patient into the Extension Study, as deemed necessary per Investigator and approved by the Medical Monitor for patient safety.

11.4.8 COVID-19 Testing

Testing for COVID-19 is not required for this study but may be implemented by the study site at any time during the study due to safety regulations or procedures. Testing for COVID-19 may be individually mandated by EGD facilities and, if this is required, will be consented through the site and not listed in the AK002-003X informed consent form.

12. Evaluations and Procedures by Visit

Written, informed consent will be obtained before any study procedure is performed. Evaluations and procedures by visit are shown in Table 1.

All recorded clock times should utilize a 24-hour clock. Extension Day 1 is the day of the first infusion in this extension study.

12.1 Prior to Extension Day 1

The following procedures will be performed prior to Extension Day 1:

- Informed Consent.
- Collect and assess baseline safety evaluations for patients that were discontinued from AK002-003 or are >45 days from the Day 113 visit in AK002-003.
- Confirm eligibility for the study.
- Administer 60 mg oral prednisone (or approved alternative) 12–24 hours prior to predicted infusion start.

12.2 Extension Day 1 – First Day of Dosing

The following procedures will be performed prior to study drug infusion:

- Confirm eligibility for the study.
- Obtain the SF-36 Health Survey from the Day 113 visit of Study AK002-003 or newly completed for patients that were discontinued from study treatment due to high eosinophil counts or are >45 days from their Day 113 visit in AK002-003.
- Determine body weight: Obtain from the Day 113 visit of Study AK002-003 if Day 113 is the same day or day prior to Extension Day 1. If Day 113 of Study AK002-003 is more than 1 day prior to Extension Day 1, a new body weight must be obtained.
- Enter PID and weight into IRT.
- Document any changes in baseline diet: Obtain from Day 113 visit of Study AK002-003 or newly collected for patients that were discontinued from study treatment due to high eosinophil counts or are >45 days from their Day 113 visit in AK002-003.
- Collect vital signs: Obtain from Day 113 visit of Study AK002-003 or newly collected for patients that were discontinued from study treatment due to high eosinophil counts or are >45 days from their Day 113 visit in AK002-003.
- Perform symptom-directed physical examination, as needed: Obtain from Day 113 visit of Study AK002-003 or newly collected for patients that were discontinued from study treatment due to high eosinophil counts or are >45 days from their Day 113 visit in AK002-003.
- Collect blood samples for CBC, blood chemistry, ADA, and PK if not collected at the Day 113 visit of Study AK002-003 or for patients that were discontinued from study treatment due to high eosinophil counts or are >45 days from their Day 113 visit in AK002-003. Differential cell counts from Day 113 in AK002-003 will remain blinded.
- Collect urine for urinalysis: Obtain from the Day 113 visit of Study AK002-003 or newly collected for patients that were discontinued from study treatment due to high eosinophil counts or are >45 days from their Day 113 visit in AK002-003.
- Collect urine and perform urine pregnancy test if patient is of childbearing potential.
- The study pharmacist will prepare study drug at 1 mg/kg using the body weight obtained at the visit. The final combined volume of the intravenous bag of study drug + 0.9% NaCl will be **120** mL.

  Note: A volume of **100 mL** of the calculated dose of study drug will be administered to the patient. The extra 20 mL is to be used to prime the intravenous infusion line during the preparation of the intravenous line at the bedside.

Procedures associated with the infusion of study drug include:

- Infuse 100 mL of study drug over at least 4 hours using an infusion pump. See Pharmacy Manual for Infusion Rates. Record the start and stop times of the infusion including any times the infusion is interrupted.
- Collect vital signs 15 (±5) minutes after the start of infusion.
- An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

The following procedures will be performed after study drug infusion:

- Collect vital signs immediately following (+5 minutes) the end of infusion.
- Collect CBC with differential 1 hour (±15 minutes) after the end of infusion.
- Observe the patient for 1 to 4 hours after the end of infusion.

Concomitant medication use and AE (including AESI and SAE) will be documented throughout the clinic visit.

12.3 Extension Day 29 (±3)

The following procedures will be performed prior to study drug infusion:

- Have patient complete the SF-36 Health Survey.
- Have patient complete PGIC Questionnaire.
- Determine body weight.
- Enter PID and weight into IRT.
- Document any changes in diet from last study visit.
- Collect vital signs.
- Collect urine and perform urine pregnancy test if patient is of childbearing potential.
- Perform symptom-directed physical examination, as needed.
- Collect blood samples for CBC, blood chemistry and ADA.
- The study pharmacist will prepare study drug at 3 mg/kg using the body weight obtained at the visit. The final combined volume of the intravenous bag of study drug + 0.9% NaCl will be 120 mL.

Procedures associated with the infusion of study drug include:

- Premedication may be administered at the Investigator's discretion, in discussion with the Medical Monitor for the Day 29 infusion.
- Infuse 100 mL of study drug using an infusion pump over 3 hours on Extension Day 29. See Pharmacy Manual for Infusion Rates. Record the start and stop times of the infusion including any times the infusion is interrupted.

The following procedures will be performed after study drug infusion:

- Collect vital signs immediately following (+5 minutes) the end of infusion.
- Collect CBC with differential 1 hour (±15 minutes) after the end of infusion.
- Observe the patient for at least 1 hour after the end of infusion.

Concomitant medication use and AE (including AESI and SAE) will be documented throughout the clinic visit.

12.4 Extension Day 57 (±3) to Extension Day 197 (±3)

The following procedures will be performed on Extension Days 57, 85, 113, 141, 169, and 197 (±3 days).

The following procedures will be performed prior to study drug infusion:

- Have patient complete the PGIC questionnaire on Extension Day 57 and Day 85 only.
- Have patient complete the SF-36 Health Survey.
- Determine body weight.
- Enter PID and weight into IRT.
- Document any changes in diet.
- Collect vital signs.
- Collect urine and perform urine pregnancy test if patient is of childbearing potential.
- Perform symptom-directed physical examination, as needed.
- Collect blood samples for CBC, blood chemistry and ADA.
- The study pharmacist will prepare study drug at 3 mg/kg using the weight obtained at the visit.

Procedures associated with the infusion of study drug include:

- Premedication may be administered at the Investigator's discretion, in discussion with the Medical Monitor for Day 57–Day 197 infusions.
- Infuse 100 mL of study drug using an infusion pump over at least 1 to 4 hours, depending on Investigator's discretion and tolerance to prior infusions. See Pharmacy Manual for Infusion Rates. Record the start and stop times of the infusion including any times the infusion is interrupted.
- Collect vital signs 15 (±5) minutes after the start of infusion.
- An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

The following procedures will be performed after study drug infusion:

- Collect vital signs immediately following (+5 minutes) the end of infusion.
- Collect CBC with differential 1 hour (±15 minutes) after the end of infusion.
- Observe the patient for at least 1 hour after the end of each infusion.

Concomitant medication use and AE (including AESI and SAE) will be documented throughout the clinic visit.

12.5 Extension Day 211 (±3)

All risks and associated details regarding the EGD procedure will be discussed with the patient by the EGD provider.

- Patient should arrive fasting for the EGD procedure, as specified by instructions from the EGD provider.
- Collect AE, SAE, and changes in concomitant medications. Capture all concomitant medications provided to the patient during the EGD.
- Perform the EGD with biopsy following procedures provided by Allakos and all EGD facility SOPs.

12.6 Extension Day 225 (±3) to Extension Day 533 (±3)

The following procedures will be performed on Extension Days 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, and 533 (±3 days).

The following procedures will be performed prior to study drug infusion:

- Have patient complete the SF-36 Health Survey.
- Determine body weight.
- Enter PID and weight into IRT.
- Document any changes in diet.
- Collect vital signs.
- Perform urine pregnancy test if patient is of childbearing potential.
- Perform symptom-directed physical examination, as needed.
- Collect blood samples for CBC, blood chemistry, and ADA. ADA should only be collected on dosing days through Extension Day 365 and on Extension Day 533.
- The study pharmacist will prepare study drug at 3 mg/kg using the weight obtained at the visit.

Procedures associated with the infusion of study drug include:

- Premedication may be administered at the Investigator's discretion, in discussion with the Medical Monitor.
- Infuse 100 mL of study drug using an infusion pump over at least 1 to 4 hours, depending on Investigator discretion and tolerance to prior infusions. See Pharmacy Manual for Infusion Rates. Record the start and stop times of the infusion including any times the infusion is interrupted.
- Collect vital signs 15 (±5) minutes after the start of infusion.
- An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

The following procedures will be performed after study drug infusion:

- Collect vital signs immediately following (+5 minutes) the end of infusion.
- Collect CBC with differential 1 hour (±15 minutes) after the end of infusion.
- Observe the patient for 1 to 4 hours after the end of infusion.

Concomitant medication use and AE (including AESI and SAE) will be documented throughout the clinic visit.

12.7 Extension Day 547 (±3)

All risks and associated details regarding the EGD procedure will be discussed with the patient by the EGD provider.

- Patient should arrive fasting for the EGD procedure, as specified by instructions from the EGD provider.
- Collect AE, SAE, and changes in concomitant medications. Capture all concomitant medications provided to the subject during the EGD.
- Perform the EGD with biopsy following procedures provided by Allakos and all EGD facility SOPs.

12.8 Extension Day 561 (±3) to Extension Day 701 (±3)

The following procedures will be performed on Extension Days 561, 589, 617, 645, 673, and 701 (±3 days).

The following procedures will be performed prior to study drug infusion:

- Have patient complete the SF-36 Health Survey.
- Determine body weight.
- Enter PID and weight into IRT.
- Document any changes in diet.
- Collect vital signs.
- Perform urine pregnancy test if patient is of childbearing potential.
- Perform symptom-directed physical examination, as needed.
- Collect blood samples for CBC and blood chemistry.
- The study pharmacist will prepare study drug at 3 mg/kg using the weight obtained at the visit.

Procedures associated with the infusion of study drug include:

- Premedication may be administered at the Investigator's discretion, in discussion with the Medical Monitor.
- Infuse 100 mL of study drug using an infusion pump over at least 1 to 4 hours, depending on the Investigator's discretion and tolerance to prior infusions. See Pharmacy Manual for Infusion Rates. Record the start and stop times of the infusion including any times the infusion is interrupted.

- Collect vital signs 15 (±5) minutes after the start of infusion.
- An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

The following procedures will be performed after study drug infusion:

- Collect vital signs immediately following (+5 minutes) the end of infusion.
- Collect CBC with differential 1 hour (±15 minutes) after the end of infusion.
- Observe the patient for at least 1 hour after the end of infusion.

Concomitant medication use and AE (including AESI and SAE) will be documented throughout the clinic visit.

12.9 Extension Day 701 + 28 (±3) days *Only* if Previous Doses were Missed

The following procedures will be performed on all Infusion Days after Day 701 – ***only*** relevant if previous doses were missed – until a total of 26 doses have been received.

The following procedures will be performed prior to study drug infusion:

- Have patient complete the SF-36 Health Survey.
- Determine body weight.
- Enter PID and weight into IRT.
- Document any changes in diet.
- Collect vital signs.
- Perform urine pregnancy test if patient is of childbearing potential.
- Perform symptom-directed physical examination, as needed.
- Collect blood samples for CBC and blood chemistry.
- The study pharmacist will prepare study drug at 3 mg/kg using the weight obtained at the visit.
- Procedures associated with the infusion of study drug include:
- Premedication may be administered at the Investigator's discretion, in discussion with the Medical Monitor.

- Infuse 100 mL of study drug using an infusion pump over at least 1 to 4 hours, depending on the Investigator's discretion and tolerance to prior infusions. See Pharmacy Manual for Infusion Rates. Record the start and stop times of the infusion including any times the infusion is interrupted.
- Collect vital signs 15 (±5) minutes after the start of infusion.
- An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

The following procedures will be performed after study drug infusion:

- Collect vital signs immediately following (+5 minutes) the end of infusion.
- Collect CBC with differential 1 hour (±15 minutes) after the end of infusion.
- Observe the patient for at least 1 hour after the end of infusion.

Concomitant medication use and AE (including AESI and SAE) will be documented throughout the clinic visit.

12.10 Follow-up Extension Day 729 (±3) or 28 (±3) Days after Last Dose, if ET or if Missed Doses are being made up

All risks and associated details regarding the EGD procedure will be discussed with the patient by the EGD provider.

- Patient should arrive fasting for the EGD procedure, as specified by instructions from the EGD provider.
- Collect AE, SAE, and changes in concomitant medications. Capture all concomitant medications provided to the patient during the EGD.
- Perform the EGD with biopsy following procedures provided by Allakos and all EGD facility SOPs.

For Early Termination: Perform EGD 28 (±3) days after the last dose of study drug or prior to this, if necessary, to ensure compliance with the visit. If patient discontinues the study more than 28 days after the last dose of study drug, perform the EGD as soon as possible.

12.11 Follow-up Extension Day 736 (±3) or 35 (±3) Days after Last Dose, if ET or if Missed Doses are being made up

Procedures for Extension Day 736 or 35 (±3) days after last dose of study drug, include:

- Determine body weight.
- Collect vital signs.
- Have patient complete the SF-36 Health Survey.
- Document any changes in diet.
- Perform symptom-directed physical examination, as needed.
- Collect blood samples for CBC, blood chemistry, PK, and ADA.
- Collect urine for urinalysis and perform urine pregnancy test if patient is of childbearing potential.
- Instruct patient to continue completing daily ePRO questionnaire through 84 days after the last dose of study drug.

Concomitant medication use, AESI, and SAE will be documented throughout the clinic visit.

12.12 Follow-up Extension Day 757 (±3) and Day 785 (±3) or 56 and 84 (±3) Days after Last Dose, if ET or if Missed Doses are being made up

Procedures for Extension Day 757 and Day 785 or 56 (±3) days and 84 (±3) days after the last dose of study drug, include:

- Have patient complete the SF-36 Health Survey.
- Document any changes in diet.
- Collect blood sample for CBC.
- Instruct patient to continue completing daily ePRO questionnaire through 84 days after the last dose of study drug.

Concomitant medication use, AESI, and SAE, will be documented throughout the clinic visit.

13. Adverse Event Reporting and Documentation

13.1 Adverse Events

In accordance with 21 Code of Federal Regulation (CFR) 312.32(b) and International Conference on Harmonisation (ICH) Guidance E2A, 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 a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

Examples of an AE include:

- Significant worsening or exacerbation of underlying medical condition.
- Significant abnormal findings from physical examinations, vital signs or laboratory tests.

The following examples are not considered AE:

- Medical or surgical procedure, although the condition leading to the procedure is usually an adverse event.
- Anticipated day-to-day fluctuations of preexisting medical conditions (including laboratory values) as long as worsening from baseline does not occur.
- Signs or symptoms of the disorder being studied, unless they become more severe or occur with a greater frequency than occurring at baseline.

All non-serious AE that are not AESI, whether elicited by questions from study staff, volunteered, or noted on physical examination/laboratory testing, and regardless of causality or severity, will be assessed and recorded in the eCRF beginning after first administration of study drug and ending at Extension Day 785 or 84 (± 3) days after last dose of study drug if patient is early terminating or if missed doses are being made up.

13.2 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets that one of the following criteria:

- Death
- A life-threatening AE that places the patient 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 occurring in the offspring of a study patient.
- Other important medical events may also be considered a SAE when, based on appropriate medical judgment, they jeopardize the patient or require intervention to prevent one of the outcomes listed above.

Serious adverse events will be assessed and recorded after the first administration of study drug and ending at Extension Day 785 (±3) or 84 (±3) days after the last dose of study drug if patient is early terminating or if missed doses are being made up.

13.3 Adverse Events of Special Interest

Adverse events of special interest for this study include:

- Malignancies confirmed by histopathological report. (Mast cells and eosinophils are part of the normal immune response, by decreasing their function, AK002 could theoretically increase the risk of malignancy).
- Parasitic infections confirmed by positive clinical laboratory test. (Eosinophils are especially active in protecting the body from parasitic infections and decreasing their function could theoretically increase the risk of parasitic and opportunistic infections).
- Opportunistic infections (infections known to be more severe or occur more frequently in immunosuppressed populations) as confirmed by positive clinical laboratory test.
- Infusion-related reactions and hypersensitivity reactions, including anaphylaxis.

Beginning from the time of first study drug infusion and ending at Extension Day 785 (±3) or 84 (±3) days after the last dose of study drug if the patient is early terminating or if missed doses are being made up, any new AESI must be recorded in the Adverse Event eCRF and designated as an "adverse event of special interest." If new information related to any previously reported AESI is identified, the appropriate eCRF should be updated.

13.4 Infusion-Related Reactions

All AE, considered by the Investigator to be related to the infusion of the biological substance and occurring within 24 hours of the start of the study drug infusion, should be captured as 1 IRR.

Common symptoms of IRR include:

- Flushing
- Chills
- Back or abdominal pain
- Chest discomfort or tightness
- Dizziness
- Shortness of breath
- Headache

- Hypotension or hypertension
- Nausea
- Vomiting
- Sweating
- Fever
- Urticaria
- Pruritus
- Bronchospasm

All symptoms experienced by a patient during an infusion-related reaction will be listed in the eCRF under 1 infusion-related reaction, unless the Investigator believes a symptom is not part of the infusion-related reaction, in which case it will be recorded separately. The start time of the infusion-related reaction will be captured as the start time of the first symptom and the end time of the infusion-related reaction will be captured as the end time of the last symptom.

13.5 Anaphylaxis

A suspicion of anaphylaxis will be carefully monitored and treated according to standard of care. Emergency crash cart equipment and medications, including multiple doses of epinephrine, vasopressors, and bronchodilators, will be available at all times during the conduct of the study. To define anaphylactic reactions in a consistent and objective manner, all AE of suspected anaphylaxis will be evaluated using Sampson's Criteria for Anaphylaxis (Appendix 19.4). The assessment of an adverse event will be done pursuant to definitions set forth by ICH Good Clinical Practice (GCP) guidelines and applicable regulatory requirements.

If a patient experiences signs or symptoms of anaphylaxis, the patient may be treated with standard of care, such as diphenhydramine, acetaminophen, methylprednisolone, epinephrine, and other supportive measures along with cessation of the infusion.

13.6 Evaluating Adverse Events and Serious Adverse Events

13.6.1 Establishing Diagnosis

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., dysuria, urinary nitrites should be reported as a urinary tract infection). If the diagnosis is not known, individual signs and symptoms should be assessed and recorded in the Adverse Event eCRF as separate AE. The Investigator (or qualified Subinvestigator) must assign the AE attributes listed in the following sections and is responsible for ensuring their capture in the source documentation.

13.6.2 Assessment of Intensity

The Investigator will use their clinical judgment as well as the guidelines laid out in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (or most current version) tables (Table 2 and Appendix 19.3) to assess the intensity of each AE and SAE.

Table 2 Adverse Event Severity per the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0

Grade*	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening consequences, urgent intervention indicated
5	Death related to adverse event

*Grade refers to the severity of the adverse event. The CTCAE displays Grades 1 to 5 with unique clinical descriptions of severity for each AE based on this general guideline.

The term "severe" is a measure of intensity, and a severe AE is not necessarily a SAE. When the intensity of an AE changes more than once a day, the maximum severity for the event should be entered into the Adverse Event eCRF. If the intensity changes over a number of days, these changes should be recorded separately (i.e., as having distinct onset dates).

13.6.3 Assessment of Causality to Study Drug

The Investigator should use clinical judgment, as well as the guidelines in Table 3, to assess the relationship between study drug and AE.

Table 3 Adverse Event Relationship to Study Drug

Relationship to Study Drug	Comment
Related	There is clear evidence that the event is related to the use of study drug (e.g., confirmation by positive rechallenge test, if possible). Another etiology is considerably less likely.
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.

13.6.4 Assessment of Causality to Study Procedure

The Investigator should use clinical judgment as well as the guidelines in Table 4 to assess the relationship between study procedure and AE. Assessment of causality to Study Procedure should include causality to such items as EGD with biopsy or blood draw (as appropriate), or other. Infusion-related reactions should not be assessed in relation to Study Procedure, only in relation to Study Drug.

Table 4 Adverse Event Relationship to Study Procedure

Relationship to Study Procedure	Comment
Related	There is clear evidence that the event is related to a study procedure.
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 a study procedure.
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 any study procedure 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 a study procedure.

13.6.5 Action Taken

Action taken with respect to study drug will be categorized as none, study drug permanently discontinued (infusion is interrupted and is not restarted, and no subsequent infusions are given), study drug temporarily withdrawn (infusion is interrupted and is restarted, or the next infusion is still administered as planned), or other (specify).

Action taken with respect to study participation will be categorized as none, withdrawal from study participation, or other (specify).

Action taken with respect to treatment of an AE will be categorized as none, concomitant medication, concomitant procedure, or other (specify).

13.6.6 Assessment of Outcome

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

13.7 Adverse Event Reporting Procedures

13.7.1 All Adverse Events

Any clinically significant adverse event that is ongoing at the time of study completion or early termination will be followed by the Investigator until event resolution, the adverse event is otherwise explained, not considered clinically significant by the Investigator, or the patient is lost to follow-up.

All non-serious AE identified will be recorded in the Adverse Event eCRF beginning from the time of first study drug infusion and ending at Extension Day 785 or 84 (±3) days after last dose of study drug if patient is early terminating or if missed doses are made up. All SAE identified will be recorded in the Adverse Event eCRF beginning from the time of first study drug infusion and ending at Extension Day 785 or 84 (±3) days after the last dose of study drug if patient is early terminating or if missed doses are made up. Whenever appropriate, the CTCAE (version 5.0 or most current version) should be utilized for naming common AE (Appendix 19.3).

13.7.2 Serious Adverse Event Reporting

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

Serious adverse event report forms will be provided to the investigational site to assist in collecting, organizing, and reporting SAE, and forms should be completed with as much

information as is available and submitted to the Sponsor within 24 hours. Serious adverse events should also be recorded on the Adverse Event eCRF and designated as "serious."

Even when only minimal information is available for the initial SAE report, the Investigator should try to make a causality assessment, as the causality is used to determine the timing of regulatory reporting requirements. If the Investigator or designee is not available to sign the SAE report on initial submission, they should be contacted via telephone and their assessment documented on the SAE form (with a note stating signature is forthcoming).

The Investigator **may change** their causality assessment based on follow-up information and submit an amended SAE report form. All efforts will be made to obtain accurate and complete medical records for the SAE. All efforts to obtain information should be documented in the patient source documents.

The site will notify the Institutional Review Board (IRB) according to its guidelines.

The patient's condition will be followed by the Investigator or designated Subinvestigator until resolution of the condition or a return to baseline levels. If additional visits are required, the patient will be asked to return to the study site for further follow-up. If the condition is still ongoing at the time the patient exits the study, every effort will be made to continue to follow up with the patient for a reasonable period of time, as determined by the Investigator or until there is a return to baseline or stabilization of the condition. 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 SAE that have not resolved by the end of the study or that have not resolved on 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 refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Serious adverse events must be reported within 24 hours to:

Serious Adverse Event Reporting

Phone: +1 443-699-5230

Fax: +1 888-237-7475

E-mail: SAE@allakos.com

13.7.3 Pregnancy Reporting

Pregnancies are captured 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 through Extension Day 785 or 84 (±3) days after last dose of study drug if early termination or if missed doses are being made up.

Female patients must be instructed to discontinue all study drugs and inform the Investigator immediately if they become pregnant during the study. Male patients must be instructed to inform the Investigator immediately if their partner becomes pregnant during the study.

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

Any congenital abnormalities noted at birth in the offspring of a patient who received study drug will be reported as a serious adverse event. 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.

13.7.4 Adverse Event of Special Interest Reporting

Beginning from the time of first study drug infusion and ending at Extension Day 785 or 84 (±3) days after last dose of study drug if early termination or if missed doses are being made up, any new AESI (or new information related to a previously reported AESI) must be recorded in the Adverse Event eCRF and designated as an "adverse event of special interest."

An AESI that also qualifies as a SAE (per Section 13.2) must also be reported as a SAE in accordance with Section 13.7.2. Adverse events of special interest that are also SAE must be recorded in the Adverse Event eCRF and designated as both "serious" and as an "adverse event of special interest." These will be reported on the Sponsor-provided SAE forms and should be reported to the Sponsor within 24 hours of site awareness.

13.8 Medical Monitoring

Dr. Henrik Rasmussen, or appointed designee should be contacted directly using the phone number and/or email address below to report medical concerns or for questions regarding safety.

Allakos Medical Monitor
[redacted] MD, PhD
Phone: [redacted]
Email: [redacted]

13.9 Study Withdrawal Criteria

Patients will be discontinued from the study in the event that:

- Occurrence of an exclusion criterion, which is clinically relevant and affects the patient's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor.
- Rebounding of eosinophil counts to >1500/μL in patients who entered the study with eosinophil levels >1500/μL, had an IRR during the first and/or second infusions, and whose eosinophil counts were initially suppressed after study drug will be withdrawn from the study.
- Serum transaminases (alanine aminotransferase and/or aspartate aminotransferase) >3 × upper limit of normal (ULN) and total bilirubin >2 × ULN (confirmed by subsequent repeat) without an alternative explanation.
- Elevation of alanine aminotransferase or aspartate aminotransferase >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, and rash.

13.10 Study Stopping Rules

The study may be discontinued prematurely in the event of any of the following:

- A life-threatening AE that is possibly or probably related to treatment.
- A fatal AE that is possibly or probably related to treatment.
- New information leading to unfavorable risk-benefit judgment of the study drug.
- Sponsor's decision that continuation of the study is unjustifiable for medical or ethical reasons.
- Discontinuation of development of the Sponsor's study drug.

Health Authorities and IRBs will be informed about the discontinuation of the study in accordance with applicable regulations. The study may be terminated or suspended on request of Health Authorities or Sponsor.

14. Discontinuation and Replacement of Patients

14.1 Definition of Study Completion

A patient who completes 26 total infusions of study drug and follow-up visits through Extension Day 785 (±3) or 84 (±3) days after last dose or if skipped doses are being made up will be recorded as having completed the study.

14.2 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 withdraws consent.
- Adverse event 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.
- Participation in any other trial during the duration of this trial.
- Use of a non-permitted concomitant drug, without prior approval from the Medical Monitor.
- 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.

If a patient is withdrawn from treatment due to an adverse event, 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 drug treatment should be encouraged to continue on study and complete assessments and procedures according to Table 1, if possible.

Reasonable attempts will be made by the Investigator to provide reasons for patient withdrawals. The reason for the patient's withdrawal from the study will be specified in the source documents.

15. Statistical Methods and General Considerations

This section outlines the nature and rationale for the statistical methods to be used for the analysis of the data from the study. A separate Statistical Analysis Plan will describe data handling and statistical techniques in full detail. The Statistical Analysis Plan will contain any modifications to the analysis plan described below.

All patient data will be listed. When appropriate, summary statistics of number of non-missing values, mean, median, standard deviation, minimum, and maximum will be computed for continuous variables and summary statistics of number and percentage will be computed for categorical variables. No formal statistical inferences will be made. No imputation will be used for missing data.

15.1 Sample Size

Approximately 60 patients will be enrolled.

15.2 Data Sets Analyzed

All patients who have received study medication will be included in the Safety population for safety analysis.

15.3 Demographic and Baseline Characteristics

The following demographic and baseline variables will be summarized:

- Demographics
- Extension Day 1 predose vital signs and laboratory tests

15.4 Patient Disposition

The number and percent of patients who complete or discontinue from the study will be summarized. The reasons for study discontinuation will be included in the summary.

15.5 Analysis of Safety Endpoints

Adverse Events: All AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA system organ class and preferred term. Listings will include all AE collected on study. The summaries of AE will be based on TEAE, defined as an AE reported in the clinical database with a date of onset (or worsening) on or after the start date of the first intravenous infusion of the study medication.

Patient incidence (N and %) of TEAEs will be summarized as follows:

- Overview of TEAE to include
  - Number (%) of patients who report at least 1 TEAE overall, by severity and by relationship
  - Number (%) of patients who report at least 1 serious TEAE
  - Number (%) of patients who report at least 1 TEAE leading to treatment discontinuation
  - Number (%) of patients who report at least 1 TEAE of special interest
- TEAE by preferred term
- TEAE by system organ class and preferred term
- TEAE by maximum severity, system organ class, and preferred term
- Drug-related TEAE by system organ class and preferred term
- TEAE leading to withdrawal by system organ class and preferred term
- Serious TEAE by system organ class and preferred term
- TEAE of special interest by system organ class and preferred term

Clinical Laboratory Assessments: Samples will be obtained for the clinical laboratory tests identified in Section 11.4, and laboratory tests to be summarized include blood chemistry, hematology, urinalysis, and ADA.

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.

Vital Signs: Vital signs will be summarized at baseline, each visit, and change from baseline at each visit.

Physical Examination: New or worsening symptoms in the symptom-directed physical examinations will be included in the by-patient data listings.

Concomitant Medications: All medications will be coded using the most current World Health Organization Drug Dictionary. Concomitant medications will be summarized by Anatomical Therapeutic Chemical Class and preferred term.

15.6 Pharmacodynamic/Efficacy-Related Analyses

The change from baseline to end of study in the SF-36 total and domain scores will be summarized descriptively. Change and percent change from baseline to each scheduled study visit in blood eosinophil count will be summarized descriptively.

Data from the ePRO and SF-36 from Extension Day 562 through end of study may be analyzed according to analysis plans independent of the EDC database and Statistical Analysis Plan for AK002-003X.

15.7 Patient Confidentiality

Patient identity should be confirmed by the presentation of a photo identification to ensure the correct individual is consented, screened, and enrolled (if eligible).

Only the PID, patient initials, and demographics will be recorded in the eCRF. If the patient name appears on any source document collected (e.g., hospital discharge summary), it must be removed from the document if the document will be viewed by the Sponsor or a Sponsor-contracted study vendor not permitted access to patient identifying information. 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 to inspect their medical records to verify the information collected. Patients will be informed that all personal information made available for inspection will be 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 publicly available. If the results of the trial are published, the patient's identity will remain confidential.

At study check-in to the study site, patients will be advised not to share their study information with other patients.

16. Data Collection, Retention, and Monitoring

16.1 Data Collection Instruments

All staff at participating clinical sites 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 meeting FDA 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 Database Lock

The database will be locked in order to protect write access after the following preconditions are fulfilled:

- All records are entered in the database and all data queries are resolved.
- All AE are coded to the satisfaction of the Chief Medical Officer.
- All medications are coded to the satisfaction of the Chief Medical Officer.
- All decisions are made regarding all protocol violations.
- Written authorizations to lock the database are obtained from Allakos Clinical Data Management and the Chief Medical Officer.

16.5 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.

16.6 Availability and Retention of Investigational Records

In accordance with 21 CFR 312.62(c), GCP, and all other applicable regulatory requirements, following completion or termination of the study, the Sponsor or its designee 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 subcategories:

- Financial agreements
- Regulatory documents
- IRB Documents
- Drug Accountability
- Correspondence
- Medical Reports
- Patient Data
- Monitoring Visit Reports
- Sample case report forms and Case Report Form Guidelines

16.7 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to 21 CFR Parts 50, 56, and 312 and ICH GCP Guideline 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. As necessitated by the COVID-19 pandemic, monitoring of all appropriate study documentation may occur off-site, with remote access to study documents.

17. Administrative, Ethical, and Regulatory Considerations

The study will be conducted in a manner consistent with the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), IRB (21 CFR 56 and ICH E6), and Obligations of Clinical Investigators (21 CFR 312 and ICH E6). The Investigator must also comply with all applicable privacy regulations (e.g., the Health Insurance Portability and Accountability Act [HIPAA], European Union Data Protection Directive 95/46/EC).

17.1 Protocol Amendments

An amendment must be agreed to in writing by Allakos, Inc. and submitted to the health authority as a Clinical Trial Application/Investigational New Drug amendment. Protocol amendments cannot be implemented without prior written IRB 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 protocol amendments must also be signed by the Investigator.

17.2 Institutional Review Board

The protocol and informed consent form (ICF) will be reviewed and approved by the IRB of each participating center prior to study initiation. All SAE, regardless of causality, will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, ICF, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB'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 approval of the Investigational site must be available to Allakos prior to the shipment of study supplies to the 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.

The IRB 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; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.3 Informed Consent Form

Prior to study enrollment, all patients must consent to participate. The process of obtaining the informed consent will comply with all federal regulations, ICH requirements, and local laws.

The Investigator or designee will review the study and the ICF with each potential patient. The review will include the nature, scope, procedures, and possible consequences of participation in the study. The consent and review must be in a form understandable to the potential patient.

The Investigator or designee and the patient must both sign and date the ICF after review and before the patient can participate in the study. The patient will receive a copy of the signed and dated form, and the original will be retained in the 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 among the study Sponsor and respective site. The publication or presentation of any study results shall comply with all applicable privacy laws including but not limited to the HIPAA of 1996.

17.5 Clinical Trial Registration

This clinical trial is registered on the Clinical Trial Registry Website, www.ClinicalTrials.gov under NCT #03664960.

17.6 Payment to Patients

All patients may be compensated for participating in this study, in accordance with the payment amounts per study day stated in the patient's signed ICF approved by the IRB. If the patient is discontinued from the study prior to the last study visit, the patient will be compensated for each completed study visit on a pro rata basis, as stated in the patient's ICF. No compensation beyond what is stated in the ICF is permitted.

17.7 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1) Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights, or welfare of patients.

2) Personally conduct or supervise the study.

3) Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines.

4) Report to the Sponsor or designee any AE that occur in the course of the study, in accordance with 21 CFR Part 312.64 and ICH Guideline E2A.

5) Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

6) Maintain adequate and accurate records in accordance with 21 CFR Part 312.62 and ICH Guideline E6 and to make those records available for inspection with the Sponsor (or designee).

7) Ensure that an IRB that complies with the requirements of 21 CFR Part 56 and ICH Guideline E6 will be responsible for initial and continuing review and approval of the clinical study.

8) Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to patients or others (to include amendments and Investigational New Drug safety reports).

9) Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients.

10) Comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements listed in 21 CFR Part 312.

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19. Appendices

19.1 SF-36 Health Survey

19.2 PRO Questionnaire

19.3 Common Terminology Criteria for Adverse Events Version 5.0

19.4 Sampson's Criteria of Anaphylaxis

19.5 Additional Questions for Atopic Conditions

19.6 Patient Global Impression of Change Questionnaire

19.7 Dysphagia Symptom Questionnaire

19.8 EGD Histology Instructions

19.1 SF-36 Health Survey

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 mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

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
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

19.1 SF-36 Health Survey cont.

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

19.1 SF-36 Health Survey cont.

4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (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
a. Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

19.1 SF-36 Health Survey cont.

6. During the <u>past 4 weeks</u>, 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
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

19.1 SF-36 Health Survey cont.

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, 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…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. 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
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

19.1 SF-36 Health Survey cont.

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

19.2 PRO Questionnaire

EOSINOPHILIC GASTRITIS AND GASTROENTERITIS DISEASE PATIENT-REPORTED OUTCOME QUESTIONNAIRE

Instructions: This questionnaire asks about symptoms that people with eosinophilic gastritis (EG) and gastroenteritis (EGE) may have. **Think of the last 24 hours** and choose the number that best describes **the intensity of your own EG and EGE symptoms during that time.** *Please complete the daily diary every evening, at approximately the same time.*

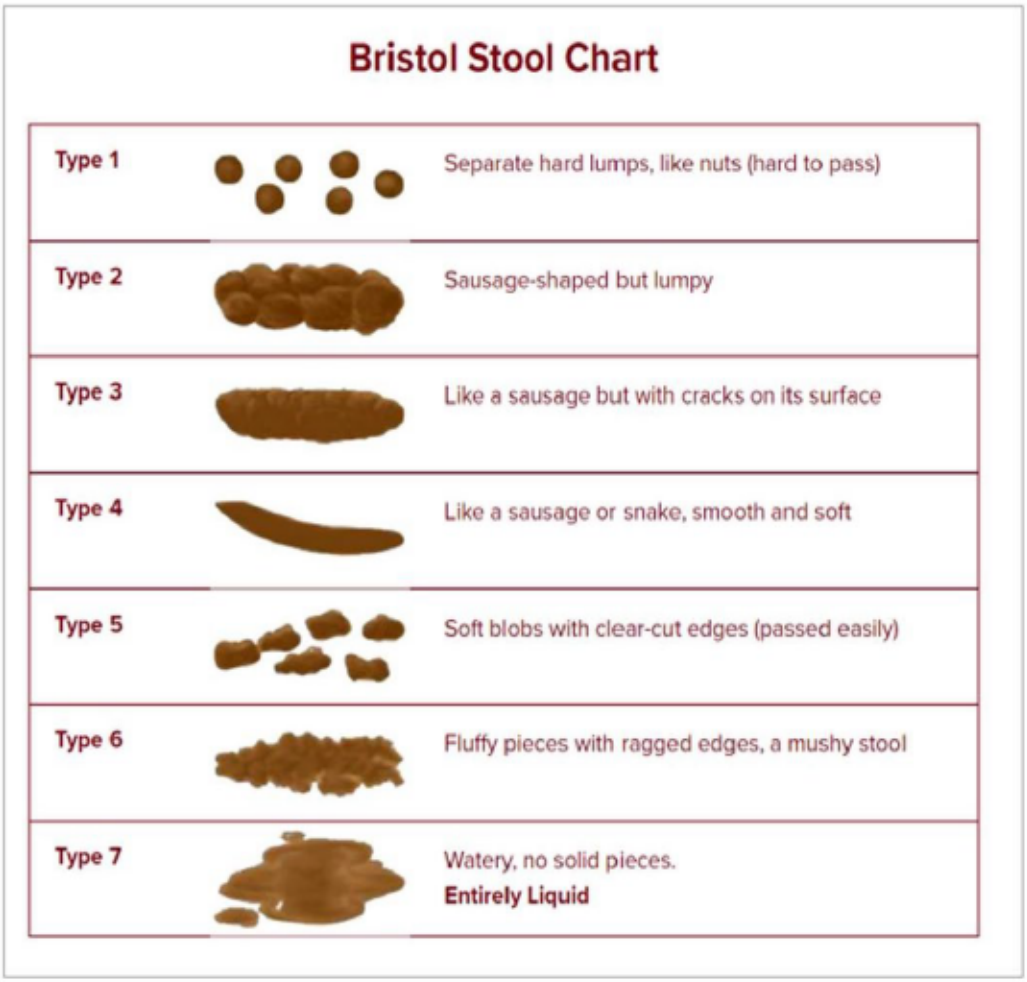
Please choose an answer by selecting only one box for each item. Answer all the items, do not skip any. If you are unsure about how to answer an item, please give the best answer you can.

1. Over the past 24 hours, please rate the intensity of your **abdominal pain** at its worst.	0 ☐ NO ABDOMINAL PAIN	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐ WORST POSSIBLE ABDOMINAL PAIN
2. Over the past 24 hours, please rate the intensity of your **nausea** at its worst.	0 ☐ NO NAUSEA	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐ WORST POSSIBLE NAUSEA
3. Over the past 24 hours, please rate the intensity of your **vomiting** at its worst.	0 ☐ NO VOMITING	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐ WORST POSSIBLE VOMITING
4. Over the past 24 hours, how many times did you **vomit**?	[patient to enter number]										
5. Over the past 24 hours, please rate the intensity of your **fullness before finishing a meal**.	0 ☐ NO EARLY FULLNESS BEFORE FINISHING A MEAL	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐ COMPLETE FULLNESS BEFORE FINISHING A MEAL
6. Over the past 24 hours, please rate the intensity of your **loss of appetite** at its worst.	0 ☐ NO LOSS OF APPETITE	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐ COMPLETE LOSS OF APPETITE
7. Over the past 24 hours, please rate the intensity of your **abdominal cramping** at its worst.	0 ☐ NO ABDOMINAL CRAMPING	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐ WORST POSSIBLE ABDOMINAL CRAMPING

19.2 PRO Questionnaire cont.

8. Over the past 24 hours, please rate the intensity of your **bloating** at its worst.	0 ☐ NO BLOATING 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ WORST POSSIBLE BLOATING
9. Over the past 24 hours, how many times did you have diarrhea (defined as **type 6 or 7 stools** on the Bristol Stool Chart)? Click for Bristol Stool Chart.	[patient to enter number]
10. Over the past 24 hours, please rate the intensity of your **diarrhea** (defined as type 6 or 7 on the Bristol Stool Chart) at its worst.	0 ☐ NO DIARRHEA 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ WORST POSSIBLE DIARRHEA

19.2 PRO Questionnaire cont.



19.3 Common Terminology Criteria for Adverse Events Version 5.0

The full CTCAE Manual can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

Example of Grading for Infusion-Related Reactions

Adverse Event	General Disorders and Administration Site Conditions				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					

Example of Grading for Laboratory Abnormalities

Adverse Event	Grade				
	1	2	3	4	5
Growth hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	–	–	–
Definition: A finding based on laboratory test results that indicate abnormal levels of growth hormone in biological specimen.					
Haptoglobin decreased	<LLN	–	–	–	–
Definition: A finding based on laboratory test results that indicate a decrease in levels of haptoglobin in a blood specimen.					
Hemoglobin increased	Increase in >0–2 mg/dL above ULN or above baseline if baseline is above ULN	Increase in >2–4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if base is above ULN		
Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin in a biological specimen.					
INR increased	>1–1.5 × ULN; >1–1.5 times above baseline if on anticoagulation	>1.5–2.5 × ULN; >1.5–2.5 times above baseline if on anticoagulation	>2.5 × ULN; >2.5 times above baseline if on anticoagulation	–	–
Definition: A finding based on laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample in the blood.					
Lipase increased	>ULN –1.5 × ULN	>1.5–2.0 × ULN	>2.0–5.0 × ULN	>5.0 × ULN	–
Definition: A finding based on laboratory test results that indicate an increase in the level of lipase in a biological specimen.					
Lymphocyte count decreased	<LLN–800/mm^3; <LLN–0.8 × 10e9/L	<800–500/mm^3; <0.8–0.5 × 10e9/L	<500–200/mm^3; <0.5–0.2 × 10e9/L	<200/mm^3; <0.2 × 10e9/L	–
Definition: A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.					
Lymphocyte count increased	–	>4000/mm^3–20,000/mm^3	>20,000/mm^3	–	–
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.					

19.4 Sampson's Criteria of Anaphylaxis

ANAPHYLAXIS: Sampson's definition of anaphylaxis (clinical definition) is the acute onset of illness (minutes to several hours) which involves **SKIN, MUCOSAL TISSUE, or BOTH** (e.g., generalized hives, pruritus or flushing, swollen lips-tongue uvula) **with 1 OR more of the following** (Sampson, 2006):

- **RESPIRATORY:** Airway compromise (e.g., dyspnea, wheeze, or bronchospasm, stridor, reduced PEF, hypoxemia)
- **CIRCULATORY:** Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope)

OR

2 or MORE of the following that occur rapidly after exposure:

- **SKIN, MUCOSAL TISSUE:** e.g., generalized hives, itch-flush, swollen lips-tongue-uvula
- **RESPIRATORY:** Airway compromise (e.g., dyspnea, wheeze, or bronchospasm, stridor and reduced PEF)
- **CIRCULATORY:** Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope)
- **GASTROINTESTINAL:** Persistent gastrointestinal symptoms (e.g., Crampy abdominal pain, vomiting, nausea, diarrhea)

19.5 Additional Questions for Atopic Conditions

ADDITIONAL QUESTIONS FOR SUBJECTS WITH ATOPIC CONDITIONS

This questionnaire asks about symptoms that people with your condition may have. **Think of the last 24 hours only** and choose the number that best describes **the intensity of your symptoms during that time.**

Please choose an answer by selecting only one box per question.

Question # 1 **Answer ONLY** if you have a history of atopic (allergic) asthma	Over the past 24 hours, please rate the severity of symptoms of asthma at its worst ☐ 0 – No asthma symptoms ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 – Worst possible asthma symptoms
Question # 2 **Answer ONLY** if you have a history of atopic dermatitis	Over the past 24 hours, please rate the severity of symptoms of atopic dermatitis at its worst ☐ 0 – No atopic dermatitis symptoms ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 – Worst possible atopic dermatitis symptoms
Question # 3 **Answer ONLY** if you have a history of eosinophilic esophagitis (EoE)	Over the past 24 hours, please rate the severity of difficulty swallowing (dysphagia) at its worst ☐ 0 – No difficulty swallowing ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 – Worst possible difficulty swallowing

19.6 Patient Global Impression of Change Questionnaire

Allakos AK002-003X
Patient Global Impression of Change (PGIC) Questionnaire

Directions for Subject: Please mark one answer for each question.

1. Please choose the response below that best describes the change in your overall symptoms since the time of your last study visit (about one month ago):
   - ☐ Very Much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very Much Worse

2. Please choose the response below that best describes the change in your abdominal pain since the time of your last study visit (about one month ago):
   - ☐ Very Much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very Much Worse

3. Please choose the response below that best describes the change in your nausea since the time of your last study visit (about one month ago):
   - ☐ Very Much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very Much Worse

4. Please choose the response below that best describes the change in your diarrhea since the time of your last study visit (about one month ago):
   - ☐ Very Much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very Much Worse

19.7 Dysphagia Symptom Questionnaire

AK002-003X
Dysphagia Symptom Questionnaire (version 4.0)
and score for each response option

Question	Response options	Score
1. Since you woke up this morning, did you eat solid food?[b]	No	–
	Yes	–
2. Since you woke up this morning, has food gone down slowly or been stuck in your throat?	No	0
	Yes	2
3. For the most difficult time you had swallowing food today (during the past 24 hours), did you have to do anything to make the food go down or to get relief?	No, it got better or cleared up on its own	0
	Yes, I had to drink liquid to get relief	1
	Yes, I had to cough and/or gag to get relief	2
	Yes, I had to vomit to get relief	3
	Yes, I had to seek medical attention to get relief	4
4. The following question concerns the amount of pain you have experienced when swallowing food. What was the worst pain you had while swallowing food over the past 24 hours?[c]	None, I had no pain	0
	Mild	1
	Moderate	2
	Severe	3
	Very Severe	4

DSQ Dysphagia Symptom Questionnaire
[a]The scoring algorithm was constructed from responses to questions 2 and 3, to ensure that the final DSQ score was driven by the frequency and severity of dysphagia
[b]Responses to question 1 were unscored
[c]Responses to question 4 were not included as part of the psychometric analysis; question 4 is a standalone item on the DSQ

19.8 EGD Histology Instructions

See Central Histology Manual for details about collecting, labeling, and shipping specimens.

Staining

The performance of the evaluations listed below will require the following stains for each biopsy set:

- Esophagus: 1) H&E; 2) tryptase; 3) trichrome
- Stomach: 1) H. pylori immunostain; 2) H&E; 3) tryptase; 4) trichrome
- Duodenum: 1) H&E; 2) tryptase; 3) trichrome

Biopsies will be obtained from the following:

- Esophagus (only if subject has concomitant EoE)
  - A set of 2 fragments from the distal esophagus.
  - A set of 2 fragments from the mid-proximal esophagus.
  - Up to 2 extra specimens may be collected if there are any additional areas of interest.
- Stomach
  - A set of 4 specimens from separate areas of the gastric antrum (2–5 cm proximal to the pylorus).
  - A set of 4 specimens from separate areas of the gastric corpus (2 from the proximal lesser curvature and 2 from the greater curvature).
  - Up to 2 extra specimens may be collected if there are any additional areas of interest.

  Duodenum
  - 4 fragments of duodenal mucosa from the second and third part of the duodenum.
  - Up to 2 extra specimens may be collected if there are any additional areas of interest.

Note: Any stored tissue from biopsies of the esophagus, stomach, or duodenum may be used for exploratory analysis.

The following will be reported for esophageal biopsies:

- Maximum number of eosinophils per hpf.
- Maximum number of tryptase-positive mast cells per hpf.

In addition, the following histopathologic parameters will be graded from 0 (absent) to 3 (marked or severe):

19.8 EGD Histology Instructions cont.

- eosinophilic microabscesses
- eosinophilic degranulation
- basal zone hyperplasia
- spongiosis
- subepithelial tissue present (Y/N)
- *lamina propria* fibrosis (grade only if subepithelial tissue is present)

The following will be reported for gastric biopsies:

- Confirmation of absence of H. *pylori*. A highly sensitive monoclonal immunohistochemical stain will be used. If negative, then the patient can be included in the study, and the following histopathologic parameters will be graded using the Sydney System from 0 (absent) to 3 (marked or severe) for all except eosinophil counts.
  - Maximum number of eosinophils per hpf
  - Maximum number of tryptase-positive mast cells per hpf
  - Active inflammation
  - Chronic inflammation
  - Intestinal metaplasia
  - Atrophy
  - Reactive gastropathy

The following will be reported for duodenal biopsies:

- Maximum number of eosinophils per hpf
- Maximum number of tryptase-positive mast cells per hpf
- Duodenal intraepithelial lymphocytosis (with counts per 100 enterocytes when count is >20)
- Villous architecture