An Extension Study of Lirentelimab in Eosinophilic Gastritis and/or Eosinophilic Duodenitis (Formerly Referred to as Eosinophilic Gastroenteritis)

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Clinical Research Protocol AK002-016X

A Phase 3, Multicenter, Open-Label, Extension Study to Evaluate the Efficacy and Safety of AK002 in Patients that were Previously Enrolled in AK002-016 or AK002-012 Studies and have Eosinophilic Gastritis and/or Eosinophilic Duodenitis (formerly referred to as Eosinophilic Gastroenteritis)

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	Amendment 1 15 July 2021
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Investigational Product	AK002
Study Phase	3
Sponsor	Allakos Inc. 825 Industrial Road, Suite 500, San Carlos, CA 94070
Medical Monitor	Name: [redacted], MD Telephone: [redacted] Email: [redacted]

Approval: [redacted]

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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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Amendment 2: **23 March 2022**

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(s)
AESI	Adverse event(s) of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
C	Centigrade
CBC	Complete blood count
CFR	Code of Federal Regulation
cm	Centimeter
COVID-19	Coronavirus disease of 2019
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
DSQ	Dysphagia Symptom Questionnaire
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
ET	Early termination
Ext	Extension
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HES	Hypereosinophilic Syndrome
HIPAA	Health Insurance Portability and Accountability Act
hpf	High-power field
ICE	Intercurrent events

ICF	Informed consent form
ICH	International Conference on Harmonisation
IgE	Immunoglobulin E
IgG1	Immunoglobulin G1
IP	Investigational product
IRB	Institutional Review Board
IRR	Infusion related reaction
IRT	Interactive response technology (system)
ISM	Indolent systemic mastocytosis
IV	Intravenous
kg	Kilogram
LARC	Long-Acting Reversible Contraceptives
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MTD	Maximum tolerated dose
NaCl	Sodium chloride
NCS	Not clinically significant
NK	Natural killer
PGIC	Patient Global Impression of Change
PID	Patient identification number
PK	Pharmacokinetic(s)
SAE	Serious adverse event(s)
SF-36	Short-Form Health and Well Being Survey
Siglec	Sialic acid-binding, immunoglobulin-like lectin
TEAE	Treatment-emergent adverse event(s)
TSS	Total Symptom Score
ULN	Upper limit of normal
USP	United States Pharmacopeia
w/v	Weight/volume
WFI	Water for Injection
WHODD	World Health Organization Drug Dictionary
WOCBP	Women of childbearing potential

1. Protocol Synopsis

Study Title	A Phase 3, Multicenter, Open-Label, Extension Study to Evaluate the Efficacy and Safety of AK002 in Patients That Were Previously Enrolled in AK002-016 or AK002-012 Studies and have Eosinophilic Gastritis and/or Eosinophilic Duodenitis (formerly referred to as Eosinophilic Gastroenteritis)
Sponsor	Allakos Inc., 825 Industrial Road, Suite 500, San Carlos, CA 94070 USA
Number of Sites	Approximately 60 clinical centers in the United States and Australia
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. In blood, binding of AK002 to Siglec-8 induces antibody-dependent cellular cytotoxicity (ADCC) against eosinophils, leading to rapid and sustained depletion of these cells from the circulation. In the tissue, AK002 induces direct apoptosis of eosinophils and inhibition of mast cells.
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 (EGE) in previous studies. Multiple doses of 3 mg/kg have been given to patients with ISM, CU, severe AC, 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 pharmacokinetic (PK) parameters demonstrating a half-life amenable to administration every 4 weeks. To date, 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 reaction (IRR). Most IRR were mild to moderate and resolved on their own, with no treatment required; IRR that were serious, resolved within approximately 24 hours. In all studies there was a transient decrease in lymphocyte count after the AK002 infusion (usually resolving within 1 day) that was not associated with any clinical consequence and a sustained suppression of eosinophils that was consistent with the mechanism of action of AK002. No significant trends were observed for changes in vital signs, electrocardiograms (ECG), clinical laboratory parameters, or physical examination.

Clinical Background cont.	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 for patients on placebo ($p<0.0001$). The reduction of eosinophils was associated with a statistically significant reduction in total symptom score 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 ($p<0.0001$). Approximately 40% of patients had concomitant eosinophilic esophagitis (EoE). In those patients, a mean reduction of 95% of eosinophils/high-power field (hpf) in esophageal biopsies for AK002 was observed versus no change for placebo. Also, 13 of 14 AK002-treated patients (93%) were histologic responders as defined by ≤6 eosinophils/hpf versus 1 of 9 placebo-treated patients (11%). Dysphagia improved by 53% in AK002-treated patients versus 17% in placebo treated patients. More than 90% of patients in the Phase 2 study elected to continue into a long-term extension study (AK002-003X). In that study, a starting dose of 1 mg/kg was followed by doses of 3 mg/kg. Premedication of 80 mg oral prednisone was administered the day before the first and second doses for 20 of the 58 patients enrolled. Using this premedication regimen, no IRR were reported on the first infusion of AK002 in the Phase 2 extension study. A total of 38 patients have been treated for at least 72 weeks in the AK002-003X extension study. The drug has been well tolerated, and no consistent long-term drug-related adverse events (AE) have been noted.
Target Disease Background and Rationale	EG and/or EoD represent what are traditionally 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).

Target Disease Background and Rationale cont.	The diagnosis is 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 is more appropriate. 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, fullness before finishing a meal, 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 quality 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 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 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 markedly 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, and EG/EoD, the proposed AK002 dose regimen is 18 total doses of 3 mg/kg AK002 administered every 4 weeks. To date, a range of AK002 doses from 0.0003 mg/kg to 10 mg/kg have been tested and the maximum tolerated dose (MTD) has not been reached. 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). Both regimens produced dramatic reduction in tissue eosinophils and were associated with substantial improvement in symptoms. However, numerically greater improvements were observed in the high dose arm compared with the low dose arm. As there were no differences in safety and tolerability between the 2 dosing regimens and the higher dose regimen appeared to be more effective, the 3 mg/kg dose was selected as the starting dose in this Phase 3 open-label extension study.
Number of Patients	Up to approximately 183 patients could be enrolled, based on enrollment of Study AK002-016.
Study Design	This is a Phase 3, multicenter, open-label, extension study to evaluate the safety and efficacy of AK002 in patients that were previously enrolled in AK002-016 or AK002-012 studies and have EG and/or EoD. In addition, this study provides the option of active treatment in patients who received placebo in the double-blind, placebo-controlled, randomized AK002-016 study. Patients enrolled in the study will receive up to 18 infusions of AK002 administered every 4 weeks and will be followed for 12 weeks after last dose. During the Extension Study AK002-016X, patients will maintain the same patient number that was assigned in Study AK002-016 and Study AK002-012, as applicable. 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 (including adverse events of special interest and serious adverse events). In addition, blood samples will be obtained for evaluation of PK and anti-drug antibodies (ADA). The study is designed as follows: • Patients completing Study AK002-016 dosing and entering the extension study may begin extended dosing 1 day after the Day 176 visit of Study AK002-016, which will be considered Day 1 of Study AK002-016X. • Patients entering the extension study but who cannot start the extension study 1 day after the Day 176 visit has occurred will remain in the main study until they receive the first dose of study drug in the extension study.

Study Design cont.	• The Day 197 and Day 225 main study visits will occur if the patient does not enroll in the extension study prior to the scheduled date of these visits. A patient enrolling in the extension study prior to Day 197 will not complete the Day 197 or Day 225 procedures under the main study. • A patient not enrolled in the extension study on or before Day 225 will not be able to enter the extension study. • Patients entering the extension study within 28 (±3) days of the last study visit in AK002-016 will not require duplicate predose labs or procedures prior to the first dosing in AK002-016X. • Patients will receive monthly infusions of AK002 administered every 28 (±3) days in an open-label manner. All infusions of AK002 will be administered at 3 mg/kg. • An EGD with biopsy will occur on Day 211 (±3) and Day 505 (±3) or 28 (±3) days after last dose of study drug if early termination (ET). • Patients will be followed for 84 (±3) days after last dose. Follow-up safety visits will occur on Extension Days 512, 533, and 561 (±3 days) or 35, 56, and 84 (±3) days after last dose if ET from the study. If only 1 follow-up visit is possible, the EGD with biopsy and first safety follow-up visit (Day 35 after last dose) may be combined. If a patient does not agree to have the early-termination EGD, the first safety follow-up visit (Day 35 after last dose) should still occur. • 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 AK002-016 and will be asked to maintain the same diet through the first 6 months of the study. After the seventh dose has been administered, diet and eating habits may be liberalized, as desired, with all changes noted in the CRF. • Prestudy medications should remain unchanged throughout the study. Systemic or swallowed steroids above 10 mg daily prednisone (or equivalent) will not be allowed except as an approved premedication prior to infusion, to treat an IRR that occurs during infusion, or the use is due to unforeseen circumstances when it is deemed medically necessary to treat an unrelated medical condition. • Daily administration of the PRO questionnaire (including any appropriate additional questions) throughout the study and follow-up period for all patients. • Total duration of Study AK002-016X will be approximately 21 months.

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 AK002-016 or Study AK002-012. This study also provides patients randomized to placebo in Study AK002-016 the option to receive active dosing.
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 adverse events, vital signs, laboratory tests, changes in concomitant medication use due to adverse events, immunogenicity, and other safety parameters.
Pharmacodynamic/ Efficacy Endpoints	• Short-Form Health and Well Being Survey (SF-36) questionnaire • Gastrointestinal symptomatology (EG/EoD PRO questionnaire) • Change in blood eosinophil count • Change in eosinophil counts in gastric and/or duodenal biopsies
Study Population	Patients who complete Study AK002-016 or Study AK002-012 will have the option to receive AK002 in an open-label manner. A patient is categorized as having completed Study AK002-016 if 6 infusions of study drug are administered and the patient is followed at least through the Day 176 visit for AK002-016. Patients are followed under the AK002-016 study until they receive their first dose in the AK002-016X study. A patient is categorized as having completed Study AK002-012 if the patient received all cohort-appropriate doses and was followed for 5 months after the last dose of study drug in AK002-012.
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 AK002-016, defined as having received 6 infusions of study drug and followed through at least Day 176 (±3 days) or completed Study AK002-012, defined as having received the cohort-appropriate number of doses and followed for 5 months after last dose of study drug. 3) If patient is on preexisting dietary restrictions, willingness to maintain those restrictions until the seventh dose has been received. After the seventh dose, diet may be liberalized. 4) Able and willing to comply with all study procedures.

Patient Selection Criteria cont.	**Inclusion Criteria cont.** 5) Female patients must be either postmenopausal 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 (vasectomy is acceptable) 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) Planned or expected vaccination with live attenuated vaccines during the treatment, or vaccination expected within 5 half-lives (4 months) of AK002 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.

Test Product, Dose, and Administration	AK002 ([redacted]) is supplied as a sterile liquid and will be diluted with 0.9% sodium chloride (NaCl) for intravenous injection. The injection will be administered by IV infusion as specified in the Pharmacy Manual. AK002 is formulated in [redacted] pH 6.0, in Water for Injection (WFI). There is no placebo in this study. AK002 at a dose of 3 mg/kg will be prepared according to the patient's body weight. Dosing will occur every 28 (±3) days for a total of 18 monthly doses. Dosing will occur on Days 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, and 477 (±3 days). Twelve to 24 hours prior to the first infusion of AK002, 80 mg oral prednisone will be self-administered by the patient. A steroid premedication prior to the start of any subsequent infusions may only be administered with the written approval of the Medical Monitor. The initial infusion should be given over at least a 4-hour period. The second and subsequent infusions can be given over at least a 2-hour period, depending on the patient's tolerance of the previous infusions and at the Investigator's discretion. After the sixth infusion, a 1-hour infusion rate may be utilized. Any changes in the infusion rate schedule due to tolerability will not be considered deviations from the protocol, as long as the maximum infusion speed is not exceeded/increased beyond the protocol specified limits. All infusions must be completed within 8 hours of AK002 being mixed with NaCl.
Duration of Patient Participation	The total study duration for each patient will be approximately 21 months. This includes: • Treatment period of approximately 18 months • Post-treatment follow-up period of 84 days (±3 days) following last dose of AK002.
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 study completion, Day 561 (±3) or 84 (±3) days after last dose if ET. Severity of AE will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE 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.

Safety Evaluations cont.	Additional safety evaluations include vital signs, CBC with differential, blood chemistry, urinalyses, symptomatic physical examinations, and anti-drug antibodies (ADA) to AK002.
Pharmacodynamic/ Efficacy Evaluations	Daily self-administration of a disease-specific Patient Reported Outcome (PRO) questionnaire will be used to evaluate signs and symptoms associated with EG and/or EoD. Patient Total Symptom Score (TSS) will be evaluated, capturing 6 common symptoms of EG/EoD (abdominal pain, nausea, abdominal cramping, loss of appetite, fullness before finishing a meal [early satiety], and bloating). Vomiting and diarrhea will also be captured but will not be included in the TSS. For patients with concomitant allergic asthma or atopic dermatitis, evaluation will include a question for each about the severity of symptoms over the past 24 hours. For all patients that received the dysphagia question during AK002-016, the daily evaluation will also include a question about the severity of dysphagia over the past 24 hours. Patients will rate their quality of life using the non-disease-specific SF-36 at various study visits. Biopsies of gastric and duodenal mucosa collected during pre-treatment and post-treatment EGD will be evaluated for number of eosinophils. In addition, the number of eosinophils in esophageal mucosa will be evaluated in patients with concomitant EoE. Blood eosinophil counts will be assessed at each study visit, predose and 1 hour postdose.
Pharmacokinetic Evaluations	Blood (serum) will be collected for assessment of AK002 concentration using a validated enzyme-linked immunosorbent assay method. Blood (serum) will be collected for assessment of AK002 ADA using a validated assay method. The PK and ADA blood samples will be obtained predose on Extension Day 1 (***or*** obtained from the Day 176, 197, or 225 evaluations of Study AK002-016 if the patient enters AK002-016X) as well as on Extension Day 197 (±3) and Day 512 (±3) or 35 (±3) days after last dose of study drug if ET. 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.

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 IgE-mediated anaphylaxis in this transgenic mouse line, indicating that Siglec-8 is pharmacologically active in the model. The ability of AK002 to effect 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-dose 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 IV administration of 50 mg/kg or 100 mg/kg, respectively. 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 (NOAEL) following IV 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 referred to as eosinophilic gastroenteritis (EGE) in previous studies.

Multiple doses of 3 mg/kg have been given to patients with ISM, CU, severe AC, 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 a half-life amenable to administration every 4 weeks.

To date, healthy volunteers and patients with ISM, CU, severe AC, EG/EoD, eosinophilic esophagitis (EoE), and mast cell gastritis have been enrolled in clinical studies. In general,

AK002 has been well tolerated. The most common treatment-emergent adverse event (TEAE) observed was infusion-related reaction (IRR). Most IRR were mild to moderate and resolved on their own, with no treatment required. Infusion-related reactions that were serious resolved within approximately 24 hours. Common symptoms of IRR were headache, nausea, sweating, flushing, and redness. Most IRR occurring during the infusion could be managed by slowing or temporary interruption of the infusion, with minimal intervention. In 6 healthy volunteers who received 2 doses of 0.3 mg/kg AK002, 4 weeks apart, the second dose was better tolerated than the first dose. This is 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 all studies there was a transient decrease in lymphocyte count after the AK002 infusion (usually resolving within 1 day) that was not associated with any clinical consequence and a sustained suppression of eosinophils that was consistent with the mechanism of action of AK002. No significant trends were observed for changes in vital signs, electrocardiograms (ECG), clinical laboratory parameters, or physical examinations.

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 for the high dose and low dose AK002-treated patients, respectively, versus a 10% increase for placebo-treated patients ($p<0.0001$). The reduction of eosinophils was associated with a statistically significant reduction in total symptom score (TSS) of 58% in the high dose AK002 group and 49% reduction in the low dose AK002 group versus a 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 ($p<0.0001$).

Approximately 40% of patients had concomitant EoE. In those patients, a mean reduction of 95% of eosinophils/hpf in esophageal biopsies for AK002-treated patients was observed versus no change for placebo-treated patients. Also, 13 of 14 AK002-treated patients (93%) were histologic responders as defined by ≤6 eosinophils/hpf versus 1 of 9 placebo-treated patients (11%). Dysphagia improved by 53% in AK002-treated patients versus 17% in placebo-treated patients.

More than 90% of patients in the Phase 2 study elected to continue into a long-term continuation study. In that study, a starting dose of 1 mg/kg AK002 was used, followed by subsequent doses of 3 mg/kg AK002. Premedication of 80 mg prednisone was administered the day before the first dose and second dose for 20 of the 58 patients dosed. Using this premedication regimen, no IRR were observed on the first infusion of the extension study.

A total of 38 patients have been treated for at least 72 weeks in the AK002-003X extension study. The drug has been well tolerated, and no consistent long-term drug related AE have been noted.

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 other cause of the eosinophilia (Caldwell, 2014).

Eosinophilic gastritis and/or eosinophilic duodenitis (formerly referred to as eosinophilic gastroenteritis) represent what are traditionally 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 the stomach and small intestine (Prussin, 2014; Reed, 2015; Zhang, 2017). The diagnosis is 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 is more appropriate. 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, fullness before finishing a meal, 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 ages 1–64 years old). 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 qualify of life and contribute 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 include dietary restriction/elimination, proton pump inhibitors (PPI), antihistamines, systemic or topical 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 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 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 markedly 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 show significant improvement 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, and EG/EoD, the proposed AK002 dose regimen of 18 total doses is 3 mg/kg administered every 4 weeks. To date, a range of AK002 doses from 0.0003 mg/kg to 10 mg/kg have been tested, and the maximum tolerated dose (MTD) has not been reached.

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 0.3, 1, 3, and 3 mg/kg). Both regimens produced dramatic reduction in tissue eosinophils and were associated with substantial improvement in symptoms. However, numerically greater improvements were observed in the high dose arm compared with the low dose arm.

As there were no differences in safety or tolerability between the 2 dosing regimens and the higher regimen appeared to be more effective, the 3 mg/kg dose was selected for this Phase 3 open-label extension study.

The infusions were generally well tolerated at all doses with most IRR being mild to moderate and very few AE outside the infusion window. Patients with ISM, CU, severe AC, mast cell gastritis, and EG/EoD have received monthly doses of 1 mg/kg and 3 mg/kg AK002. Subsequent infusions in multiple dose cohorts were associated with fewer IRR when compared with the first infusion.

4. Study Objectives

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 AK002-016 or Study AK002-012. In addition, this study provides patients randomized to placebo in AK002-016 the option to receive active dosing.

5. Study Design

5.1 Study Overview

This is a Phase 3, multicenter, open-label, extension study to evaluate the safety and tolerability of AK002 in patients with EG and/or EoD.

Patients who complete Study AK002-016 or Study AK002-012 will have the option to receive AK002 in an open-label manner. A patient is categorized as having completed Study AK002-016 if 6 infusions of study drug are administered and the patient is followed through at least Day 176 (±3 days). A patient is categorized as having completed Study AK002-012 if the patient received all cohort-appropriate doses and was followed for 5 months after last dose of study drug in AK002-012. During Study AK002-016X, patients will maintain the same patient number that was assigned in Study AK002-016 or Study AK002-012, as applicable.

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 PK and ADA.

The study is designed as follows:

- Patients completing Study AK002-016 dosing and entering the extension study may begin extended dosing 1 day after the Day 176 visit of Study AK002-016, which will be considered Extension Day 1 of Study AK002-016X.

- Patients entering the extension study but who cannot start the extension study 1 day after the Day 176 visit has occurred will remain in the main study until they receive the first dose of study drug in the extension study.
- The Day 197 and Day 225 main study visits will occur if the patient does not enroll in the extension study prior to the scheduled date of these visits. A patient enrolling in the extension study prior to Day 197 will not complete the Day 197 or Day 225 procedures under the main study.
- A patient not enrolled in the extension study on or before Day 225 in the AK002-016 study will not be able to enter the extension study.
- Patients entering the extension study within 28 (±3) days of the last study visit in AK002-016 will not require duplicate predose labs or procedures prior to the first dosing in AK002-016X.
- Patients will receive up to 18 infusions of AK002 administered every 28 (±3) days in an open-label manner. All infusions of AK002 will be administered at 3 mg/kg.
- An EGD with biopsy will occur on Day 211 (±3) and Day 505 (±3) or 28 (±3) days after last dose of study drug if early termination (ET).
- Patients will be followed for 84 (±3) days after last dose. Follow-up safety visits will occur on Extension Days 512, 533, and 561 (±3 days) or 35, 56, and 84 (±3) days after last dose if ET from the study. If only 1 follow-up visit is possible, the EGD with biopsy and first safety follow-up visit (Day 35 after last dose) may be combined. If a patient does not agree to have the early-termination EGD, the first safety follow-up visit (Day 35 after last dose) should still occur.
- The extension study does not include fasting requirements, except for those required for the conduct of EGD. Patients underwent a standardized baseline evaluation of eating habits, food habits/restrictions, and food avoidance behaviors during Study AK002-016 and will be asked to maintain the same diet through the first 6 months of the study. After the seventh dose has been received, diet and eating habits may be liberalized, as desired, with all changes that occur noted in the CRF.
- Prestudy medications should remain unchanged throughout the study. Systemic or swallowed steroids above 10 mg daily prednisone (or equivalent) will not be allowed except as an approved premedication prior to infusion, to treat an IRR that occurs during infusion, or the use is due to unforeseen circumstances when it is deemed medically necessary to treat an unrelated medical condition.

- Daily administration of the PRO questionnaire (including any appropriate additional questions) throughout the study and the follow-up period for all patients.
- Total duration of Study AK002-016X will be approximately 21 months.

5.2 Schedule of Events

The overall schedule of procedures and assessments are depicted in Table 1.

Table 1 Schedule of Assessments

Assessments	Prior to First Dose	Extension Treatment Period (18 months)					Extension Follow-Up Period (12 weeks)			
		Dose 1	Doses 2–7	Dose 8	Day 211	Doses 9–18	EGD Follow-up	Follow-up #1	Follow-up #2	Follow-up #3
		Extension Day 1	Day 29, 57, 85, 113, 141, 169 (±3 days)	Day 197 (±3 days)	(±3 days)	Day 225, 253, 281, 309, 337, 365, 393, 421, 449, 477 (±3 days)	Day 505 (±3 days) or 28 days after last dose if ET	Day 512 (±3 days) or 35 days after last dose if ET	Day 533 (±3 days) or 56 days after last dose if ET	Day 561 (±3 days) or 84 days after last dose if ET
Informed consent	X									
Medical History[1]		X								
Prior/Concomitant Medications[2]		X[3]	X	X	X	X	X	X	X	X
Baseline Diet Assessment/ Compliance		X[3]	X	X		X		X	X	X
Body weight[4]		X(predose)[3]	X (predose)	X (predose)		X (predose)		X	X	X
Vital signs[5]		X	X	X		X		X	X	X
Symptom-directed Physical Exam[6]		X[3]	X	X		X		X	X	X
Eligibility assessment	X	X								
ePRO Training and Activation[7]		X								
ePRO Questionnaire (may include additional questions)[8]		<----------Perform daily from Day 1 through Day 561 or 84 days after last dose, if ET---------->								
SF-36 Health Survey[9]		X[3]	X	X		X		X	X	X
Dysphagia Question		<----------Perform daily from Day 1 through Day 561 or 84 days after last dose, if ET---------->								
Dipstick Pregnancy Test[10]		X[3] (predose)	X (predose)	X (predose)		X (predose)		X		
Access IRT to enter Patient ID and current body weight[11]		X (predose)	X (predose)	X (predose)		X (predose)				
Premedication: prednisone[12]	X[21]									
Study drug administration[13]		X[22]	X	X		X				

Table 1 Schedule of Assessments cont.

Assessments	Prior to First Dose	Extension Treatment Period (18 months)					Extension Follow-Up Period (12 weeks)			
		Dose 1	Doses 2–7	Dose 8	Day 211	Doses 9–18	EGD Follow-up	Follow-up #1	Follow-up #2	Follow-up #3
		Extension Day 1	Day 29, 57, 85, 113, 141, 169 (±3 days)	Day 197 (±3 days)	(±3 days)	Day 225, 253, 281, 309, 337, 365, 393, 421, 449, 477 (±3 days)	Day 505 (±3 days) or 28 days after last dose if ET	Day 512 (±3 days) or 35 days after last dose if ET	Day 533 (±3 days) or 56 days after last dose if ET	Day 561 (±3 days) or 84 days after last dose if ET
Blood for CBC with differential[14,15]		X	X	X		X		X	X	X
Blood for chemistry[14,16]		X (predose)[3]	X (predose)	X (predose)		X (predose)		X	X	X
Urinalysis[14,17]		X (predose)[3]		X (predose)				X		
Blood for pharmacokinetics[14,18]		X (predose)[3]		X (predose)				X		
Blood for ADA[14,19]		X (predose)[3]		X (predose)				X		
Blood for Total Serum IgE[14,20]		X (predose)[3]						X		
EGD with biopsy[23]					X		X			
Non-serious adverse events[24]		X	X	X	X	X	X	X	X	X
Adverse events of special interest[25]		X	X	X	X	X	X	X	X	X
Serious adverse events[26]		X	X	X	X	X	X	X	X	X

CBC: Complete Blood Count EGD: Esophago-Gastro-Duodenoscopy ET: Early Termination IRT: Interactive Response Technology

Table Notes

1) Record all pertinent, ongoing medical history as well as any significant adverse events (AE) that occurred in the AK002-016 or AK002-012 study but resolved before the first dose in the extension study.

2) Record all concomitant medications taken within 30 days of Extension Day 1 and during the course of the study. Record all concomitant medication received during EGD, any premedication given, and any medication used for the treatment of IRR.

3) Do not collect if procedure was performed as part of the last study visit in AK002-016 (on Day 176, 197 or 225, depending on when patient receives first dose in AK002-016X). Differential cell counts collected for Study AK002-016 will not be unblinded. The AK002-016X postdose CBC with differential is still required 1 hour (±15 minutes) after the first AK002-016X infusion ends.

Table Notes cont.

4) Body weight will be measured predose and recorded in kilograms (kg) on Day 1, all infusion days, and at Follow-up visits on Days 512, 533, and 561 or 35 (±3), 56 (±3), and 84 (±3) days after last dose of study drug if ET. Body weight is to be measured in kg as it is used to determine patient dosing calculations

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 within 30 minutes predose, within 30 minutes after the start of infusion, and within 30 minutes following the end of infusion.

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

7) Activate PRO questionnaire and provide patient with unique username and password. Use ePRO Teaching Tool for patient training and reference. PRO questionnaire should be activated for all patients on Day 1.

8) The PRO should be completed by the patient, around the same time each day using ViedocME electronic portal. Patients with concomitant history of asthma and/or atopic dermatitis symptoms will receive an extra question about each, as appropriate. If the dysphagia question was populated in AK002-016, it will continue to populate in the daily ViedocME questions for AK002-016X. The PRO may be completed via paper if electronic access is not possible.

9) Completed in clinic by the patient (complete prior to blood draw, physical examination, or vital sign measurements) during study visits, using ViedocME electronic portal. May be completed via paper if electronic access is not possible.

10) A small amount of urine collected for urinalysis will be used for dipstick pregnancy test (for women of childbearing ability) predose on all infusion days and on Day 512 (±3) or 35 (±3) days after last dose if ET. Test kits will be supplied by the central laboratory. Tests will be completed on site and evaluated prior to infusion.

11) Endpoint IRT to be used to assign kit numbers for each patient dosing. Current patient body weight (taken day before infusion or day of infusion) will be entered into IRT and amount of AK002 to be mixed with 0.9% NaCl will be calculated via Endpoint.

12) All patients will self-administer 80 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.

13) Study drug will be administered as a single peripheral IV infusion over at least a 4-hour period for Dose 1. Second and subsequent infusions can be given over at least a 2-hour period, depending on prior infusion tolerability. After the sixth infusion a 1-hour infusion schedule may be used. Refer to the Pharmacy Manual.

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

15) Blood for CBC with differential, including absolute blood eosinophil count, will be obtained just prior to each infusion, 1 hour (±15 minutes) after the end of each infusion as well as on Extension Days 512, 533, and 561 (±3 days) or 35, 56, and 84 (±3) days after last dose of study drug if ET.

16) Blood for Chemistry will be obtained just prior to each infusion as well as on Extension Days 512, 533, and 561 (±3) or 35, 56, and 84 (±3) days after last dose of study drug if ET.

17) Urine for Urinalysis will be collected on Extension Days 1, 197 (±3), and 512 (±3) or 35 (±3) days after last dose of study drug if ET.

Table Notes cont.

18) Blood for PK will be collected on Extension Days 1, 197 (±3), and 512 (±3) or 35 (±3) days after last dose of study drug if ET.

19) Blood for ADA will be collected on Extension Days 1, 197 (±3), and 512 (±3) or 35 (±3) days after last dose of study drug if ET. ADA will also be collected when an immunogenicity-related AE occurs.

20) Blood for Total Serum IgE will be collected on Extension Day 1 and Extension Day 512 (±3) or 35 (±3) days after last dose of study drug if ET.

21) The consent form for AK002-016X must be signed ***prior*** to the patient taking prednisone premedication for the AK002-016X study.

22) The final EGD and Day 176 hematology assessment (first safety follow-up) for AK002-016 ***must*** be collected ***prior*** to the patient taking prednisone premedication for AK002-016X. Therefore, dosing in AK002-016X must take place at least 1 day after completion of the Day 176 visit for AK002-016.

23) See Appendix 6 for biopsy assessments. EGD should occur on Day 211 (±3) and Day 505 (±3) or 28 (±3) days after last dose of study drug if the patient discontinues the study early and agrees to have an early termination biopsy.

24) Non-serious AE will be captured from Day 1 (first dose of study drug) through Day 561 (±3) or 84 (±3) days after last dose of study drug if ET.

25) Adverse events of special interest will be captured from Day 1 (first dose of study drug) through Day 561 (±3) or 84 (±3) days after last dose of study drug if ET.

26) Serious adverse events will be captured from Day 1 (first dose of study drug) through Day 561 (±3) or 84 (±3) days after last dose of study drug if ET.

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
- Changes in body weight and vital signs
- Hematology
- Changes in concomitant medication use due to AE
- Blood chemistry
- Urinalysis
- Anti-drug antibodies
- Adverse events

6.2 Pharmacokinetic Endpoints

Blood (serum) will be collected for assessment of AK002 concentrations using a validated enzyme-linked immunosorbent assay (ELISA) method. Pharmacokinetic (PK) blood samples will be obtained predose on Extension Day 1 (if not already collected for AK002-016 last study visit), predose on Extension Day 197, and also on Extension Day 512 (±3) or 35 (±3) days after last dose of study drug, if ET, for assessment of AK002 concentrations.

Blood (serum) will be collected for assessment of ADA using a validated assay method. The ADA blood samples will be obtained predose on Extension Day 1 (if not already collected for AK002-016 last study visit), predose on Extension Day 197, and also on Extension Day 512 (±3 days) or 35 (±3) days after last dose of study drug, if ET, for assessment of ADA. Extra blood (serum) samples may also be drawn for assessment of ADA, in case of an immunogenicity-suspected AE.

6.3 Efficacy Endpoints

Daily self-administration of a disease-specific Patient Reported Outcome (PRO) questionnaire will be used to evaluate signs and symptoms associated with EG and/or EoD. The PRO Total Symptom Score (TSS) will be used to evaluate efficacy and comprises 6 symptoms, as listed below:

- Abdominal pain intensity
- Nausea intensity
- Fullness before meal intensity
- Loss of appetite intensity
- Bloating intensity
- Abdominal cramping intensity

Changes in quality of life will be measured by the Short-Form Health and Well-Being 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

Up to approximately 183 patients could be enrolled in Study AK002-016X, based on the enrollment of Study AK002-016.

7.2 Study Population

Patients who complete Study AK002-016 or Study AK002-012 and meet the inclusion criteria in Section 7.3 and none of the exclusion criteria in Section 7.4 will be eligible for enrollment.

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 AK002-016, defined as having received 6 infusions of study drug and followed through at least Day 176 (±3) or completed Study AK002-012, defined as having received the cohort-appropriate number of doses and followed for 5 months after last dose of study drug.
3) If patient is on preexisting dietary restrictions, willingness to maintain those restrictions, until the seventh dose has been received. After the seventh dose, diet may be liberalized.
4) Able and willing to comply with all study procedures.

5) Female patients must be either postmenopausal 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 (vasectomy is acceptable) 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) Planned or expected vaccination with live attenuated vaccines during the treatment period, or vaccination expected within 5 half-lives (4 months) of AK002 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.

8. Concurrent Medications

Prior and concomitant medications include both prescribed and over-the-counter medications and will be recorded in the electronic Case Report Forms (eCRF). Medications taken for EG/EoD or symptoms of EG/EoD, as well as any medications taken within 30 days prior to extension study Day 1 should be recorded.

Medications taken prior to the study should be maintained, as much as possible. Patients should be advised against taking any new medication or stopping an existing medication, both prescribed and over-the-counter, without consulting the Investigator, unless the change 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 use of prohibited medications as per AK002-016 criteria).

All medications used during the conduct of the study must be documented.

8.1 Prohibited Medications

Any biologics or other medications that may interfere with the study, such as immuno-suppressive or immunomodulatory drugs (i.e., azathioprine, JAK inhibitors, 6-mercaptopurine, methotrexate, cyclosporine, tacrolimus, anti-TNF, anti-IL-5, anti-IL-5 receptor, dupilumab, anti-IgE antibodies, omalizumab) are prohibited. The use of systemic or topical corticosteroids with a dose of >10 mg/day of prednisone or equivalent is prohibited unless it is due to unforeseen circumstances when it is deemed medically necessary to treat an unrelated medical condition or when given as a premedication prior to infusion or to treat an IRR that occurs during infusion.

There may be circumstances when the use of some of these medications during the study may be acceptable. In these cases, approval must be obtained from the Allakos Medical Monitor. An EGD may not be performed or may be delayed if a prohibited medication is started during the course of the study, at the discretion of the Medical Monitor.

8.2 Allowed Medications

Medications, other than those that are prohibited (Section 8.1), such as antihistamines, PPI, leukotriene antagonists, and sodium cromolyn are allowed during the study and, unless required due to unforeseen medical necessity, doses are to remain stable.

Systemic or swallowed corticosteroids with a dose of ≤10 mg/day prednisone or equivalent are acceptable, as long as the dose remains stable throughout the study. The use of systemic or topical corticosteroids with a dose of >10 mg/day of prednisone or equivalent is permitted if it is deemed to be medically necessary to treat an unrelated medical condition or when given as a premedication prior to infusion or to treat an IRR that occurs during infusion.

There may be circumstances when it is deemed medically necessary to alter (or start/stop) the dose of an allowed medication. If this medication is used to treat an unrelated medical condition, it is not a deviation from the protocol.

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 WFI.

***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 minimum fill volume of approximately 10 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 the 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 the 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 and Dose Regimen

All infusions of AK002 will be 3 mg/kg. Dosing will occur on Extension Days 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, and 477 (±3 days).

The exact amount of AK002 to be mixed with NaCl 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. 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 AK002 is first mixed with NaCl.

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 should be kept open before and after the infusion with sufficient quantities of 0.9% NaCl to assure patency.

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 2 hours on Extension Days 29 (±3), 57 (±3), 85 (±3), 113 (±3), and 141 (±3) and over at least 1 hour from Extension Day 169 (±3) and onwards. 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 mL to 101 mL will be considered a complete infusion and will not be recorded as a deviation of the study.

Due to programming limitations of some infusion pumps, all volumes associated with the infusion may be rounded to the nearest $1/10^{th}$ mL.

For the first infusion of study drug, patients will be premedicated with 80 mg oral prednisone (or approved equivalent) 12–24 hours prior to the start of the study drug infusion. For subsequent infusions, premedication may only be used at the discretion of the Investigator and with the written approval of the Medical Monitor.

The IV infusion may be interrupted and/or the rate may be reduced if a patient has an IRR. The time 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 at least 1 hour after the end of each infusion, as per Investigator discretion.

9.7 Study Drug Storage

AK002 will be stored by the study sites at 2º–8ºC in a secured, restricted, and temperature-monitored location in the designated pharmacy, pending drug preparation. The 0.9% NaCl will be stored at ambient temperature, per manufacturer's requirements. 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, it will be reported to the Sponsor using the guidelines in the Pharmacy Manual. The Sponsor will notify the site if the study drug is to be quarantined or can be used.

9.8 Temperature Excursions

AK002 is stable at 2°–8°C. In case of temperature excursion during shipping, or if the temperature of drug storage in the pharmacy exceeds or falls below 2°–8°C, please contact Allakos immediately by sending the completed Site Temperature Excursion Form to clinsupply@allakos.com (email) or 1-800-783-3734 (fax) before any use of the investigational product (IP). Attach all available information with the Site Temperature Excursion Form including temperature logs showing the extent and duration of the excursion.

The IP exposed to the temperature excursion should be quarantined until Allakos determines whether the IP is compromised or approved for use. Allakos or designee will provide written instructions regarding use of the IP, and these instructions should be added to the pharmacy study file.

9.9 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 form, should be used to capture receipt, dispensing, and return (or destruction). Electronic IP 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.

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 AK002-016 or Study AK002-012. The patient will maintain the same PID throughout the study.

A patient is considered enrolled in the AK002-016X study when the subject receives the first dose of open-label AK002.

10.2 Stratification and Randomization

There will be no randomization or stratification 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, depicting the required testing procedures 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.
- Physical examinations (if needed) can be performed, and urine samples can be collected either before or after other evaluations.

11.1 Dietary and Lifestyle Restrictions

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 AK002-016 and Study AK002-012 and will be asked to maintain the same diet through the first 6 months of the study. After the seventh dose has been received, diet and eating habits may be liberalized as desired, with all changes noted in the CRF.

11.2 Pharmacodynamic/Efficacy-Related Procedures

11.2.1 EG/EoD PRO Questionnaire

An electronic version of the PRO questionnaire (Appendix 1) will be completed daily at approximately the same time of day, by the patient, throughout the study.

Patients will not be able to complete a questionnaire more than 24 hours after it is due and will only be able to go back and make corrections or changes to the data originally entered with the approval of the Investigator and EDC vendor. The PRO information will be automatically captured and maintained in the ePRO system of the EDC.

A paper version of the PRO questionnaire is available to patients in case they are not able to complete the electronic version for a short period of time. Only 1 PRO should be completed per day, and the recall period should not be any more than approximately 24 hours long. The information will be manually captured and entered into the EDC by the study site.

If patients have a history of concomitant atopic dermatitis or asthma, an extra question will be populated for each relevant condition on the PRO website for the patient to complete daily. A paper version of these questions is available if the website is not accessible or the patient does not have Internet access (Appendix 5). Additionally, patients that received the dysphagia question in the AK002-016 study will continue to receive the question in the extension study.

11.2.2 Short Form-36 Health and Well-Being Survey

An electronic version of the SF-36 Health and Well-Being Survey (Appendix 2) will be completed by the patient on all dosing days (predose), as well as on extension Days (±3) 512, 533, and 561 or 35, 56, and 84 (±3) days after last dose of study drug if ET.

If the questionnaire was already completed within the last 28 days as part of the last study visit in the AK002-016 study, a duplicate entry is not required on extension Day 1.

A paper version of this questionnaire will also be available for completion in case the electronic questionnaire is not available to the patient. This information will be entered into the EDC by the study site.

11.2.3 Complete Blood Count with Differential

Blood will be obtained for CBC with differential predose and 1 hour (±15 minutes) postdose on all infusion days, as well as on Days 512 (±3), 533 (±3), and 561 (±3) or 35, 56, and 84 (±3) days after last dose of study drug if ET. If already collected within the last 28 days as part of the last study visit in the AK002-016 study, a duplicate predose collection on extension Day 1 is not

required. For patients entering the study from AK002-016, all differential cell counts will remain blinded.

The blood sample will be processed and shipped in accordance with the central 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).

11.2.4 Esophago-Gastro-Duodenoscopy with Biopsy

An EGD with biopsy will be performed on Day 211 (±3) and Day 505 (±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 laboratory (or designee) for fixing and staining. A central reader will report, among other things, maximum number of eosinophils/hpf and maximum number of tryptase-positive mast cells/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 AK002-016 will be used for comparison.

11.2.5 Baseline Diet Assessment

During the AK002-012 and AK002-016 studies, the Investigator or designee asked patients a standardized series of dietary assessment questions. The baseline diet should be maintained as much as possible through the first 6 months of the extension study even if symptoms improve. After the seventh infusion has been received, patients may liberalize their diets and make changes from the baseline diet, as desired. Changes from the baseline diet will be assessed at every study visit and 35, 56, and 84 (±3) days after last dose if ET.

11.3 Safety-Related Procedures

11.3.1 Concomitant Medications

All ongoing concomitant medications and therapies will be transferred from Study AK002-016 into Study AK002-016X. Any medications used for premedication during the conduct of the EGD or for treatment of IRR will be documented in the AK002-016X Concomitant Medications Log. Dose, route, unit, frequency of administration, indication for administration, and dates of medication will be captured. Any medication received during the study through Extension Day 561 (±3) or 84 (±3) days after last dose of study drug, if ET, will be recorded.

11.3.2 Body Weight

Body weight will be measured predose and used to determine the amount of study drug to be mixed with NaCl for each infusion. Body weight must be measured on the day of, or on the day prior to, the day of each infusion. Body weight will be entered into the interactive response technology (IRT) system for each dosing visit and will also be recorded on the Investigational Product Dose Calculation and Preparation Worksheet that the pharmacist or designee will maintain to document each patient's dose calculations.

Body weight should be collected on site on the day of each study drug infusion or on the day prior to each infusion. Body weight will also be captured on Days 512, 533, and 561 (±3) or 35, 56, and 84 (±3) days after last dose of study drug if ET.

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 all study visits through Extension Day 561 or 84 (±3) days after last dose of study drug if ET. 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 for post-infusion for which vital signs will be obtained as described below).

On dosing days, vital signs will be measured within 30 minutes predose, within 30 minutes after the start of infusion, and within 30 minutes following the end of infusion. Refer to the schedule of assessments in Table 1.

Investigators may have additional vital sign procedures performed for the purpose of treatment administration or following AE.

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 clinical safety laboratory tests.

Clinical laboratory testing may be performed locally if the site thinks the central laboratory may not be able to provide results in a timely fashion due to staff reductions, shipping issues, or other factors associated with the COVID-19 pandemic. The site will strive to use the central laboratory 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 AE 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 11.2.3. If already collected within the last 28 days as part of the last study visit in AK002-016, a duplicate predose collection on Extension Day 1 is not required for AK002-016X. The postdose collection on Day 1 is still required.

11.4.2 Blood Chemistry Profile

Blood for chemistry tests will be processed and shipped in accordance with the central laboratory manual and laboratory kit instructions.

If already collected within the last 28 days as part of the last study visit in AK002-016, a duplicate predose collection is not required on Extension Day 1. Blood will be obtained predose on all dosing days as well as on Days 512, 533, and 561 or 35, 56, and 84 (±3) days after last dose of study drug if ET.

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.

11.4.3 Pregnancy Test

For patients of childbearing potential, the site will perform a urine dipstick pregnancy (hCG) test prior to each infusion, as well as on Day 512 (±3) or 35 (±3 days) after last dose of study drug if ET. The site will perform the urine pregnancy test using an indicator stick from the pregnancy test kit supplied by the central laboratory and using urine collected for the urinalysis. This test will be assessed prior to the start of each study drug infusion. If already tested within the last 28 days as part of the last study visit in AK002-016, a duplicate test is not required on Extension Day 1. If a patient has a positive pregnancy test, dosing will immediately be discontinued.

To ensure patient safety, each pregnancy in a patient that received study drug must be reported within 24 hours of learning of its occurrence. If the patient received AK002, the pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Women who are surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months or those who are postmenopausal for at least 1 year with FSH level >30 mIU/mL are not considered to be of childbearing potential.

11.4.4 Effective Methods of Contraception for Allakos Studies

This section applies to study subjects who are women of childbearing potential (WOCBP) and male study subjects whose sexual partners are WOCBP.

Abstinence is the only birth control method that is 100% effective in preventing pregnancy. For subjects who do not practice abstinence, Allakos recommends that study subjects use highly effective methods of contraception, which include:

- **Permanent Sterilization:** Tubal ligation, vasectomy – 99% effective
- **Long-Acting Reversible Contraceptives (LARC)**:
  - IUD – 99% effective
  - Implantable rod (matchstick sized rod that contains progestin hormone implanted under the skin of the upper arm; prevents ovulation) – 99% effective
- **Contraceptive Injection:**
  - Intramuscular or subcutaneous injection of progestin hormone every 3 months – 96% effective
- **Short-Acting Hormonal Methods:**
  - Oral contraceptives or patch – 91% effective
  - Vaginal contraceptive ring (releases 2 hormones, progestin and estrogen, to prevent ovulation) – 91% effective

Note: Effectiveness rates obtained from the Birth Control Guide on the FDA web site (FDA, 2021).

Barrier and other methods not listed above when used together as dual methods such as a condom + diaphragm or condom + spermicide are less effective methods, therefore these dual methods are not recommended as they could increase the risk of becoming pregnant during the study or follow-up period. When using dual methods, at least 1 of the methods should be a highly effective method of contraception.

Subjects, who entered the study using dual methods of contraception that do not include at least 1 of the highly effective methods of contraception, are allowed to continue in the study but must be informed of the risks of not using highly effective methods of contraception.

11.4.5 Urinalysis

Urine samples will be processed and shipped in accordance with the central laboratory manual and laboratory kit instructions. Urine will be obtained on Extension Days 1, 197, and 512 or 35 (±3) days after last dose of study drug if ET. If already collected within the last 28 days as part of the last study visit for AK002-016, a duplicate collection is not required on Extension Day 1. A central laboratory will analyze the urine sample for specific gravity, pH, protein, glucose, ketones, blood, and leukocyte esterase.

11.4.6 Anti-AK002 Antibodies

Serum samples for ADA determination will be processed and shipped frozen in accordance with the central laboratory manual and laboratory kit instructions. Blood will be collected for determination of ADA predose on Extension Days 1, 197, and 512 (±3 days) or 35 (±3) days after last dose of study drug if ET. If already collected within the last 28 days as part of the last study visit in AK002-016, a duplicate collection is not required on Extension Day 1. For patients entering from Study AK002-012, a baseline collection is required prior to the first dose of study drug in AK002-016X.

A central laboratory will analyze the sample for ADA using a validated assay method. Specific information on ADA sample collection, processing, storage, and shipment will be provided in the central laboratory manual. Blood samples for ADA will also be collected anytime an immunogenicity-related AE occurs.

11.4.7 Pharmacokinetics and Storage

Blood samples for serum PK assessments will be processed and shipped frozen in accordance with the central laboratory manual and laboratory kit instructions. Blood will be collected for PK assessments predose on Extension Days 1, 197, and 512 (±3 days) or 35 (±3) days after last dose of study drug if ET. If already collected within the last 28 days as part of the last study visit in AK002-016, a duplicate predose collection is not required on Extension Day 1. For patients entering from Study AK002-012, a baseline collection is required prior to the first dose of study drug in AK002-016X.

AK002 concentrations will be determined by the central laboratory or designee using a validated ELISA method. Specific information on PK sample collection, processing, storage, and shipment will be provided in the central laboratory manual.

11.4.8 Histamine and Tryptase

If anaphylaxis is suspected, a blood sample should be obtained for plasma histamine and tryptase levels within 1–2 hours of the onset of symptoms. The sample should be sent to the central laboratory for processing.

11.4.9 IgE

Blood will be collected for determination of serum IgE levels and sent to the central laboratory for processing. Blood will be collected predose on Extension Day 1 and Day 512 (±3) or 35 (±3) days after last dose of study drug if ET. If already collected within the last 28 days as part of the last study visit in AK002-016, a duplicate predose collection is not required on Extension Day 1. For patients entering from Study AK002-012, a baseline collection is required prior to the first dose of study drug in AK002-016X.

11.4.10 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 AK002-016X informed consent form (ICF).

12. Evaluations and Procedures by Visit

Written, informed consent will be obtained before any study procedure is performed.

General Information:

- 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:

- Obtain written informed consent ***prior*** to patient receiving premedication.
- Verify eligibility for the study.
- Patient to self-administer 80 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 continuing eligibility for the study.
- Activate patient access to ViedocME website and instruct patient on use of the website to complete the questionnaire(s). Use the ePRO Teaching Tool (Appendix 4) to remind patients on the use of the electronic platform.
- Have patient complete SF-36 Health Survey. Obtain from last study visit of AK002-016 if the visit occurred within 28 days prior to Extension Day 1.
- Determine body weight (in kg).
- Enter PID and body weight (in kg) into IRT.
- Document any changes in baseline diet. Obtain from last study visit of AK002-016 if the visit occurred within 28 days prior to Extension Day 1.

- Collect vital signs within 30 minutes of the start of the infusion.
- Perform symptom-directed physical examination, as needed. Obtain from last study visit of AK002-016 if the visit occurred within 28 days prior to Extension Day 1.
- Collect blood samples for CBC, blood chemistry, IgE, ADA, and PK. Obtain from last study visit of AK002-016 if the visit occurred within 28 days prior to Extension Day 1. Differential cell counts from AK002-016 will remain blinded.
- Collect urine for urinalysis. Obtain from last study visit of AK002-016 if the visit occurred within 28 days prior to Extension Day 1.
- Perform urine pregnancy test. Obtain from last study visit of AK002-016 if the visit occurred within 28 days prior to Extension Day 1.
- The study pharmacist will prepare study drug at **3 mg/kg** using the body weight obtained at the visit or the day prior to Extension Day 1. The final combined volume of the IV bag of study drug + 0.9% NaCl will be **120 mL**.

  ***Note*: 100 mL** of the calculated volume of study drug/NaCl mixture will be administered to the patient. The extra 20 mL is to be used to prime the IV infusion line during the preparation of the IV line or to be left over in the infusion bag/tubing when the infusion is completed.

Procedures associated with the infusion of study drug include:

- Infuse 100 mL of study drug over at least 4 hours using an infusion pump. Refer to the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.
- Collect vital signs within 30 minutes after the start of infusion.
- An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected. If anaphylaxis is suspected, collect a sample of blood for plasma histamine and tryptase levels within 1–2 hours of the onset of symptoms.

The following procedures will be performed after study drug infusion:

- Collect vital signs within 30 minutes after 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.

12.3 Extension Day 29 (±3) – Dose 2

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

- Have patient complete the SF-36 Health Survey.
- Determine body weight (in kg).
- Enter PID and weight (in kg) into IRT.
- Document any changes in baseline diet.
- Collect vital signs within 30 minutes prior to the start of infusion.
- Collect urine only if patient is of childbearing potential. Conduct a urine pregnancy test.
- Perform symptom-directed physical examination, as needed.
- Collect blood samples for CBC and chemistry.
- 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 IV bag of study drug + 0.9% NaCl will be **120** mL.

  ***Note*: 100 mL** of the calculated volume of study drug/NaCl mixture will be administered to the patient. The extra 20 mL is to be used to prime the IV infusion line during the preparation of the IV line or to be left over in the infusion bag/tubing when the infusion is completed.

Procedures associated with the infusion of study drug include:

- Premedication only to be administered with the written approval of the Medical Monitor.
- Infuse 100 mL of study drug using an infusion pump over at least 2 hours on Extension Day 29. Refer to the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.
- Collect vital signs within 30 minutes after the start of infusion.
- An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected. If anaphylaxis is suspected, collect a sample of blood for plasma histamine and tryptase levels within 1–2 hours of the onset of symptoms.

The following procedures will be performed after study drug infusion:

- Collect vital signs within 30 minutes of 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) – Dose 3

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

- Have patient complete the SF-36 Health Survey.
- Determine body weight (in kg).
- Enter PID and weight (in kg) into IRT.
- Document any changes to baseline diet.
- Collect vital signs within 30 minutes prior to the start of infusion.
- Collect urine only if patient is of childbearing potential. Conduct a urine pregnancy test.
- Perform symptom-directed physical examination, as needed.
- Collect blood samples for CBC and chemistry.
- 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 IV bag of study drug + 0.9% NaCl will be **120** mL.

  ***Note*: 100 mL** of the calculated volume of study drug/NaCl mixture will be administered to the patient. The extra 20 mL is to be used to prime the IV infusion line during the preparation of the IV line or to be left over in the infusion bag/tubing when the infusion is completed.

Procedures associated with the infusion of study drug include:

- Premedication only to be administered with the written approval of the Medical Monitor.
- Infuse 100 mL of study drug using an infusion pump over at least 2 hours, depending on the Investigator's discretion and tolerance to prior infusions. Refer to the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.
- Collect vital signs within 30 minutes after the start of infusion.
- An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected. If anaphylaxis is suspected, collect a sample of blood for plasma histamine and tryptase levels within 1–2 hours of the onset of symptoms.

The following procedures will be performed after study drug infusion:

- Collect vital signs within 30 minutes of 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.

12.5 Extension Day 85 (±3) – Dose 4

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

- Have patient complete the SF-36 Health Survey.
- Determine body weight (in kg).
- Enter PID and weight (in kg) into IRT.
- Document any changes to baseline diet.
- Collect vital signs within 30 minutes prior to the start of infusion.
- Collect urine only if patient is of childbearing potential and conduct urine pregnancy test.
- Perform symptom-directed physical examination, as needed.
- Collect blood samples for CBC and chemistry.
- 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 IV bag of study drug + 0.9% NaCl will be **120** mL.

  ***Note*: 100 mL** of the calculated volume of study drug/NaCl mixture will be administered to the patient. The extra 20 mL is to be used to prime the IV infusion line during the preparation of the IV line or to be left over in the infusion bag/tubing when the infusion is completed.

Procedures associated with the infusion of study drug include:

- Premedication only to be administered with the written approval of the Medical Monitor.
- Infuse 100 mL of study drug using an infusion pump over at least 2 hours, depending on the Investigator's discretion and tolerance to prior infusions. Refer to the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.

- Collect vital signs within 30 minutes after the start of infusion.
- An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected. If anaphylaxis is suspected, collect a sample of blood for plasma histamine and tryptase levels within 1–2 hours of the onset of symptoms.

The following procedures will be performed after study drug infusion:

- Collect vital signs within 30 minutes of 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.

12.6 Extension Day 113 (±3) – Dose 5

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

- Have patient complete the SF-36 Health Survey.
- Determine body weight (in kg).
- Enter PID and weight (in kg) into IRT.
- Document any changes to baseline diet.
- Collect vital signs within 30 minutes prior to the start of infusion.
- Collect urine only if patient is of childbearing potential and perform urine pregnancy test.
- Perform symptom-directed physical examination, as needed.
- Collect blood samples for CBC and chemistry.
- 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 IV bag of study drug + 0.9% NaCl will be **120** mL.

  ***Note*: 100 mL** of the calculated volume of study drug/NaCl mixture will be administered to the patient. The extra 20 mL is to be used to prime the IV infusion line during the preparation of the IV line or to be left over in the infusion bag/tubing when the infusion is completed.

Procedures associated with the infusion of study drug include:

- Premedication only to be administered with the written approval of the Medical Monitor.
- Infuse 100 mL of study drug using an infusion pump over at least 2 hours, depending on the Investigator's discretion and tolerance to prior infusions. Refer to the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.
- Collect vital signs within 30 minutes after the start of infusion.
- An unscheduled ADA blood sample may be obtained if an immunogenicity-related adverse event is suspected. If anaphylaxis is suspected, collect a sample of blood for plasma histamine and tryptase levels within 1–2 hours of the onset of symptoms.

The following procedures will be performed after study drug infusion:

- Collect vital signs within 30 minutes of 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.

12.7 Extension Day 141 (±3) – Dose 6

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

- Have patient complete the SF-36 Health Survey.
- Determine body weight (in kg).
- Enter PID and weight (in kg) into IRT.
- Document any changes to baseline diet.
- Collect vital signs within 30 minutes prior to the start of infusion.
- Collect urine only if patient is of childbearing potential and perform urine pregnancy test.
- Perform symptom-directed physical examination, as needed.
- Collect blood samples for CBC and chemistry.
- 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 IV bag of study drug + 0.9% NaCl will be **120** mL.

***Note*: 100 mL** of the calculated volume of study drug/NaCl mixture will be administered to the patient. The extra 20 mL is to be used to prime the IV infusion line during the preparation of the IV line or to be left over in the infusion bag/tubing when the infusion is completed.

Procedures associated with the infusion of study drug include:

- Premedication only to be administered with the written approval of the Medical Monitor.
- Infuse 100 mL of study drug using an infusion pump over at least 2 hours, depending on the Investigator's discretion and tolerance to prior infusions. Refer to the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.
- Collect vital signs within 30 minutes after the start of infusion.
- An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected. If anaphylaxis is suspected, collect a sample of blood for plasma histamine and tryptase levels within 1–2 hours of the onset of symptoms.

The following procedures will be performed after study drug infusion:

- Collect vital signs within 30 minutes of 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.

12.8 Extension Day 169 (±3) – Dose 7

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

- Have patient complete the SF-36 Health Survey.
- Determine body weight (in kg).
- Enter PID and weight (in kg) into IRT.
- Document any changes to baseline diet.
- Collect vital signs within 30 minutes prior to the start of infusion.
- Collect urine only if patient is of childbearing potential and perform urine pregnancy test.

- Perform symptom-directed physical examination, as needed.
- Collect blood samples for CBC and chemistry.
- 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 IV bag of study drug + 0.9% NaCl will be **120** mL.

  ***Note*: 100 mL** of the calculated volume of study drug/NaCl mixture will be administered to the patient. The extra 20 mL is to be used to prime the IV infusion line during the preparation of the IV line or to be left over in the infusion bag/tubing when the infusion is completed.

Procedures associated with the infusion of study drug include:

- Premedication only to be administered with the written approval of the Medical Monitor.
- Infuse 100 mL of study drug using an infusion pump over at least 1 hour, depending on the Investigator's discretion and tolerance to prior infusions. Refer to the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.
- Collect vital signs within 30 minutes after the start of infusion.
- An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected. If anaphylaxis is suspected, collect a sample of blood for plasma histamine and tryptase levels within 1–2 hours of the onset of symptoms.

The following procedures will be performed after study drug infusion:

- Collect vital signs within 30 minutes of 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 197 (±3) – Dose 8

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

- Have patient complete the SF-36 Health Survey.
- Determine body weight (in kg).

- Enter PID and weight (in kg) into IRT.
- Document any changes to baseline diet. Changes are allowed after the seventh dose has occurred and will be documented in the CRF.
- Collect vital signs within 30 minutes prior to the start of infusion.
- Collect urine only if patient is of childbearing potential and perform urine pregnancy test.
- Perform symptom-directed physical examination, as needed.
- Collect blood samples for CBC, chemistry, PK, 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 IV bag of study drug + 0.9% NaCl will be **120 mL**.

  ***Note*: 100 mL** of the calculated volume of study drug/NaCl mixture will be administered to the patient. The extra 20 mL is to be used to prime the IV infusion line during the preparation of the IV line or to be left over in the infusion bag/tubing when the infusion is completed.

Procedures associated with the infusion of study drug include:

- Premedication only to be administered with the written approval of the Medical Monitor.
- Infuse 100 mL of study drug using an infusion pump over at least 1 hour, depending on the Investigator's discretion and tolerance to prior infusions. Refer to the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.
- Collect vital signs within 30 minutes after the start of infusion.
- An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected. If anaphylaxis is suspected, collect a sample of blood for plasma histamine and tryptase levels within 1–2 hours of the onset of symptoms.

The following procedures will be performed after study drug infusion:

- Collect vital signs within 30 minutes of 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 Extension Day 211 (±3) – First EGD

The on-treatment EGD should be completed 14 (±3) days after the eighth dose of study drug. All risks and associated details regarding the EGD procedure will be discussed with the patient by the EGD provider.

The following procedures will be performed:

- 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 standard operating procedures.

12.11 Extension Day 225 to Day 477 (±3) – Doses 9 to 18

Extension Days 225, 253, 281, 309, 337, 365, 393, 421, 449, and 477

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

- Have patient complete the SF-36 Health Survey.
- Determine body weight (in kg).
- Enter PID and weight (in kg) into IRT.
- Document any changes to baseline diet.
- Collect vital signs within 30 minutes prior to the start of infusion.
- Collect urine only if patient is of childbearing potential and perform urine pregnancy test.
- Perform symptom-directed physical examination, as needed.
- Collect blood samples for CBC and chemistry.
- 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 IV bag of study drug + 0.9% NaCl will be **120 mL**.

  ***Note*: 100 mL** of the calculated volume of study drug/NaCl mixture will be administered to the patient. The extra 20 mL is to be used to prime the IV infusion line during the preparation of the IV line or to be left over in the infusion bag/tubing when the infusion is completed.

Procedures associated with the infusion of study drug include:

- Premedication only to be administered with the written approval of the Medical Monitor.
- Infuse 100 mL of study drug using an infusion pump over at least 1 hour, depending on the Investigator's discretion and tolerance to prior infusions. Refer to the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.
- Collect vital signs within 30 minutes after the start of infusion.
- An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected. If anaphylaxis is suspected, collect a sample of blood for plasma histamine and tryptase levels within 1–2 hours of the onset of symptoms.

The following procedures will be performed after study drug infusion:

- Collect vital signs within 30 minutes of 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.

12.12 Extension Day 505 (±3) or 28 (±3) Days after Last Dose – Follow-up EGD

The follow-up EGD should be completed 14 (±3) days after the last dose of study drug. All risks and associated details regarding the EGD procedure will be discussed with the patient by the EGD provider.

The following procedures will be performed:

- 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 the EGD facility.

For Early Termination: Perform EGD 28 (±3) days after 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 last dose of study drug, perform the EGD as soon as possible, as directed by the Medical Monitor.

12.13 Extension Day 512 (±3) or 35 (±3) Days after Last Dose – Follow-up Visit 1

The following procedures will be performed:

- Have patient complete the SF-36 Health Survey.
- Determine body weight.
- Document any changes to baseline diet.
- Collect vital signs.
- Collect urine for all patients and perform urine pregnancy test if patient is of childbearing potential.
- Perform symptom-directed physical examination, as needed.
- Collect blood samples for CBC, chemistry, IgE, PK, and ADA.

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

For Early Termination: Perform Safety Follow-up Visit 1, 35 (±3) days after last dose of study drug or prior to this, if necessary, to ensure compliance with the visit. If patient discontinues the study more than 35 days after last dose of study drug, perform the visit as soon as possible as directed by the Medical Monitor.

12.14 Extension Day 533 (±3) or 56 (±3) Days after Last Dose – Follow-up Visit 2

The following procedures will be performed:

- Have patient complete the SF-36 Health Survey.
- Determine body weight.
- Document any changes to baseline diet.
- Collect vital signs.
- Perform symptom-directed physical examination, as needed.
- Collect blood samples for CBC and chemistry.

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

For Early Termination: Perform Safety Follow-up Visit 2, 56 (±3) days after last dose of study drug or prior to this, if necessary, to ensure compliance with the visit.

12.15 Extension Day 561 (±3) or 84 (±3) Days after Last Dose – Follow-up Visit 3

The following procedures will be performed:

- Have patient complete the SF-36 Health Survey.
- Determine body weight.
- Document any changes to baseline diet.
- Collect vital signs.
- Perform symptom-directed physical examination, as needed.
- Collect blood samples for CBC and chemistry.

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

For Early Termination: Perform Safety Follow-up Visit 3, 84 (±3) days after last dose of study drug or prior to this, if necessary, to ensure compliance with the 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 adverse event is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current 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 AE.
- 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.
- Normal progression of the disorder being studied unless it is more severe or occurs with greater speed/frequency than expected.

All AE, 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 the first administration of study drug and ending on Extension Day 561 or 84 (±3) days after last dose of study drug if ET.

The assessment of an AE will be done pursuant to definitions set forth by ICH Good Clinical Practice (GCP) guidelines and applicable regulatory requirements.

13.2 Serious Adverse Events

A SAE is defined as an AE that meets 1 of the following criteria:

- Death
- A life-threatening adverse event 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.

The date that an AE meets 1 of the criteria listed above is the date that it becomes an SAE. Conversely, the date that the SAE no longer meets 1 of the criteria listed above is the end date of the SAE. A new AE with an outcome of "recovering" may be created to address the ongoing AE once it is no longer considered serious.

Serious adverse events will be assessed and recorded after the first administration of study drug and ending on Extension Day 561 (±3) or 84 (±3) days after last dose of study drug if ET.

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 and 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.

Adverse events of special interest will be assessed beginning after the first administration of study drug and ending on Extension Day 561 (±3) or 84 (±3) days after last dose of study drug if ET. 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 AE, termed "Infusion-Related Reaction" (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 IRR will be listed in the eCRF under 1 IRR, unless the Investigator believes a symptom is not part of the IRR, in which case it will be recorded separately. The start time of the IRR will be captured as the start time of the first symptom, and the end time of the IRR will be captured as the end time of the last symptom.

Any medications used within 24 hours of an infusion for the treatment of an IRR are not considered prohibited medications nor deviations from the protocol.

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 events of suspected anaphylaxis will be evaluated using Sampson's Criteria for Anaphylaxis (Appendix 7). The assessment of an AE 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 (Table 2, Table 3, and Table 4) and is responsible for ensuring their capture in the source documentation.

13.6.2 Assessment of Intensity

The Investigator will use 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, to assess the intensity of each AE and SAE (Table 2 and Appendix 3).

Table 2 Adverse Event Severity for Adverse Events

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 AE based on the National Cancer Institute CTCAE, version 5.0, and displays Grades 1 to 5 with unique clinical descriptions of severity for each AE.

The term "severe" is a measure of intensity, and a severe AE is not necessarily a "serious" AE.

When the intensity of an AE changes more than once a day, the maximum severity of 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 AE that is ongoing at the time of study completion or ET will be followed by the Investigator until event resolution, the AE is otherwise explained, the AE is 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 on Extension Day 561 (±3) or 84 (±3) days after last dose of study drug if ET. All SAE identified will be recorded in the Adverse Event eCRF beginning from the time of first study drug infusion and ending on Extension Day 561 (±3) or 84 (±3) days after last dose of study drug if ET. Whenever appropriate, the CTCAE (version 5.0 or most current version) should be used for naming common AE (Appendix 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 must report it immediately (**within 24 hours of becoming aware of the SAE**) by telephone, fax, or email to the Sponsor, Allakos Inc.

The SAE report forms will be provided to the investigational site to assist in collecting, organizing, and reporting SAE, and the forms must be completed with as much information as is available and should be submitted to the Sponsor within 24 hours of becoming aware of the event. Serious adverse events must 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 by telephone and their assessment documented on the SAE report form (with a note stating that 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 designee 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:

SAE Reporting
Fax: +1-888-237-7475
Email: 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 561 (±3) or 84 (±3) days after last dose of study drug if ET.

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 AE or SAE, but all pregnancies in patients who received AK002 will be followed through term. For male patients with female partners who become pregnant, the site will ask the father (the study patient) to provide information about the outcome of the pregnancy and information about the baby. If detailed health information about the mother is requested by Allakos, a Pregnant Partner Information Release Form will be provided to the site for the mother to sign.

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

13.7.4 Adverse Event of Special Interest Reporting

Beginning from the time of first study drug infusion and ending on Extension Day 561 (±3) or 84 (±3) days after last dose of study drug if ET, 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. [redacted] 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.
- Serum transaminases (ALT and/or AST) >3 × upper limit of normal (ULN) ***and*** total bilirubin >2 × ULN (confirmed by subsequent repeat) without an alternative explanation.
- Elevation of ALT and/or AST >3 × ULN (confirmed by repeat) with the appearance or worsening of symptoms thought 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.
- Approval by Health Authorities of the Sponsor's study drug.

Health Authorities and IRB 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 visits through Extension Day 561 (±3) 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.
- An AE that in the opinion of the Investigator results in it being in the best interest of the patient to discontinue study treatment.
- Protocol violation requiring discontinuation of study treatment.
- Participation in any other study during the duration of this study.
- 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 AE, the patient will be followed and treated by the Investigator or designee 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 or all attempts to acquire such, 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 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

Up to approximately 183 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 TEAE will be summarized as follows:

- Overview of TEAE to include
  - Number (%) of patients who report at least one TEAE overall, by severity and by relationship
  - Number (%) of patients who report at least one serious TEAE
  - Number (%) of patients who report at least one TEAE leading to treatment discontinuation
  - Number (%) of patients who report at least one 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 weekly change in EG/EoD PRO scores from baseline TSS to Extension Day 561 or 84 (±3) days after last dose of study drug will be calculated. The change from baseline to Extension Day 561 or 84 (±3) days after last dose of study drug if ET. 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.

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's 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 study 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 adverse events 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 and/or remote 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 as permitted by individual study site requirements.

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. Each protocol amendment must also be signed by the Investigator.

17.2 Institutional Review Board

The protocol and 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 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 adversely affect the safety of the patients or the conduct of the study; an annual update and/or request for reapproval; 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.

In addition, prior to undergoing biopsies, patients will provide informed consent in accordance with the standard operating procedures and policies of the EGD facility/investigational site.

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 as NCT04620811 on the Clinical Trial Registry Website, www.ClinicalTrials.gov.

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.

After enrollment, patients at participating study sites will be compensated for each completed week of daily questionnaires as long as at least 4 questionnaires per week are completed. Patients may be reimbursed for expenses associated with attending study visits. 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 IND 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 Appendix 1: EG/EoD PRO Questionnaire

EOSINOPHILIC GASTRITIS AND DUODENITIS (formerly referred to as Gastroenteritis) DISEASE
PATIENT-REPORTED OUTCOME QUESTIONNAIRE

Instructions: This questionnaire asks about symptoms that people with eosinophilic gastritis (EG) and duodenitis (EoD) may have. **Think of the last 24 hours** and choose the number that best describes **the intensity of your own EG and EoD symptoms during that time.** *Please complete the daily diary every day, 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 (stomach) 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 (feeling like you have to throw up)** 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 (throwing up)** 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 (throw up)**?	[patient to enter number]										
5. Over the past 24 hours, please rate the intensity of your **fullness before finishing a meal** at its worst.	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 (not feeling hungry)** 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 (stomach) cramping** at its worst.	0 ☐ NO ABDOMINAL CRAMPING	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐ WORST POSSIBLE ABDOMINAL CRAMPING

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19.1 Appendix 1: EG/EoD PRO Questionnaire cont.

8. Over the past 24 hours, please rate the intensity of your **bloating (stomach feels bigger or under pressure)** 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

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19.1 Appendix 1: EG/EoD PRO Questionnaire cont.

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19.2 Appendix 2: Short Form-36 Health and Well-Being Survey Questionnaire

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

19.2 Appendix 2: Short Form-36 Health and Well-Being 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

19.2 Appendix 2: Short Form-36 Health and Well-Being Survey cont.

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

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

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

19.2 Appendix 2: Short Form-36 Health and Well-Being 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

19.2 Appendix 2: Short Form-36 Health and Well-Being 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

19.2 Appendix 2: Short Form-36 Health and Well-Being 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!

19.3 Appendix 3: Common Terminology Criteria for Adverse Events, Version 5.0

The CTCAE (version 5) for download 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

	General Disorders and Administration Site Conditions				
Adverse Event	**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

	Grade				
Adverse Event	**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.					
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 Appendix 4: ePRO Teaching Tool

PROTOCOL AK002-016
PROTOCOL AK002-016X

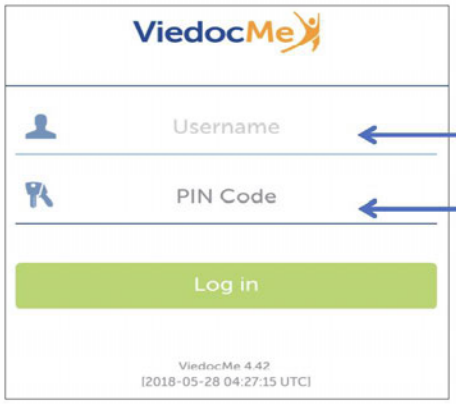
Allakos

INSTRUCTIONS FOR COMPLETION OF ELECTRONIC QUESTIONNAIRES

You are being asked to complete a ONCE DAILY 10-question EG/EoD questionnaire about your current EG or EoD (formerly referred to as EGE) symptoms, as well as other questionnaires as specified on page 3.
WEBSITE → **https://v4me.viedoc.net/Account/Login?ReturnUrl=%2F**

TO ACCESS THE ELECTRONIC QUESTIONNAIRES

- You MUST have access to the Internet in order to use the website (ViedocME) to complete the daily questionnaires. Let your study coordinator know if you expect this will be a problem for you.
- You MAY access the website from a *computer*, *smart-phone*, *tablet* or *other device* with internet service. Different devices may be used on different days to log into ViedocME and complete the questionnaires.
- The daily PRO questionnaire SHOULD BE COMPLETED around the same time each day and must be completed by 11:59PM at the latest, each day (based on your time zone). If you miss a daily questionnaire (i.e. it is not completed by 11:59PM), it will disappear and will not be available for completion. It is very important to remember to complete the daily questionnaire by 11:59PM every day.
- If you miss a daily questionnaire the next day's questionnaire will still populate. Continue answering any future questionnaires and remember to only recall your symptoms over the last 24 hours (1 day).
- During the screening period you will answer the EG/EoD PRO questionnaire and the Additional "Dysphagia" question. During the treatment period you will answer the PRO questionnaire and if you do not have other atopic conditions , only the EG/EoD PRO questionnaire will be answered daily.



LOGGING IN TO ViedocME

Enter 6-digit Username provided by Study Coordinator

Enter 4-digit PIN provided by Study Coordinator

If you forget your Username or your PIN please contact the Study Coordinator to provide/reset for you. The PIN can be reset but will not be saved by the site as you are the only one who should have access to this.

REMINDERS FROM ViedocME FOR COMPLETION OF DAILY QUESTIONNAIRES

- When the Study Coordinator sets up your ViedocME account you can choose to receive a DAILY reminder to complete your questionnaire(s) for the day. The reminder(s) will be sent if your diary entry has not been completed by 8PM each evening (in your study site time zone).
- The ViedocME reminders can be sent via Text Message and/or Email.
- *If you are Roaming outside your service area or your telephone carrier charges you per text message please be aware that you may incur charges for receiving text messages. If you prefer, the Study Coordinator can help you set up a daily alarm reminder on your personal cellular device that will ring as an alarm.*

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19.4 Appendix 4: ePRO Teaching Tool cont.

PROTOCOL AK002-016
PROTOCOL AK002-016X

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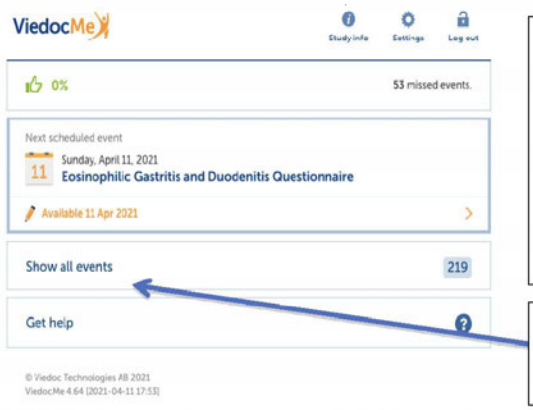
THINGS TO REMEMBER WHEN COMPLETING THE QUESTIONNAIRES

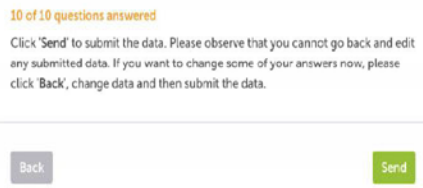
- When you first log on to ViedocME the HOME screen will display the 1st questionnaire that is due for the day, which is usually the 10-question EG/EoD Questionnaire as shown below:



Click Eosinophilic Gastritis and Duodenitis Questionnaire to complete the 10-question questionnaire for each current day. If the questionnaire for the day is LIT UP in blue it means the questionnaire is available to be completed. Upon completion, the questionnaire name will be grayed out.

Click SHOW ALL EVENTS to see all questionnaires available for a certain day

- Click SEND when you have answered all 10 questions on the daily EG/EoD PRO questionnaire:



Clicking **SEND** will submit your daily questionnaire and selecting **GO TO STARTPAGE** will take you back to the HOME screen. There are sometimes additional questionnaires that populate once the 1st questionnaire has been submitted. These questions will NOT be visible prior to the previous questionnaire being submitted/SENT for that day.

- If you have a history of atopic dermatitis (AD) and/or asthma you will have an additional question listed on your ViedocME diary EACH DAY during the screening period and during the study.
- During the screening period you will receive a question about dysphagia (trouble swallowing) and this will continue EACH DAY during the study if you have active symptoms of dysphagia.
- On study visit days you will access ViedocME to complete the SF-36 Health Survey.
- On screening Day 19 and Study days 7 and 28 you will complete the 1-question PGIS via ViedocME.
- On Study days 7 and 28 you will complete the 1-question PGIC via ViedocME.

COMPLETING THE DAILY QUESTIONNAIRES DURING THE STUDY

You will complete the EG/EoD daily questionnaire, and any additional questions as appropriate, during 3 periods of the study:

1) SCREENING period (BEFORE you receive 1st study drug)
2) TREATMENT period (WHILE you are receiving study drug)
3) FOLLOW UP period (AFTER you have completed all doses of study drug or you are withdrawing from the study early)

During the screening period the questionnaire is used to determine if your symptoms are appropriate in type and severity to be enrolled into the study. You will start completing the daily questionnaires on the first day of your participation in this study and will complete the questionnaires until the last day.

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19.4 Appendix 4: ePRO Teaching Tool cont.

PROTOCOL AK002-016
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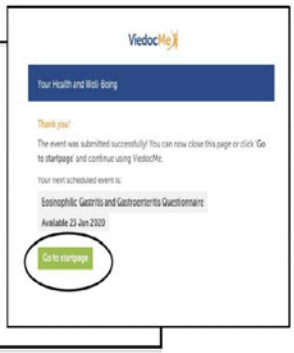
IT IS IMPORTANT:

- You complete AS MANY daily questionnaires as possible.
- You think about your symptoms in the same way throughout the whole
- study, which includes before, during and after receiving the study drug.
- You remember that each symptom should be assessed over the
- past 24 hours (1 day).
- You hit SEND after you have finished all questions on each questionnaire
- You hit GO TO STARTPAGE to see if there are any additional questions
- that need to be answered for that day.



STUDY COORDINATORS- COMPLETE THIS UPON ViedocME ACTIVATION:

Questionnaire Website: https://v4me.viedoc.net/Account/Login?ReturnUrl=%2F

Username: _____

PIN (don't share with others): _____

Daily questions to answer - Use the table below to mark which questions should be completed:

QUESTIONNAIRE	YES-during Screening	YES-during Study	NO
EG/EoD PRO questionnaire-(10) questions	X	X	
SF-36 Health Survey "Your Health and Well-Being"	X	X (ONLY DURING STUDY VISITS)	
*"Additional Question"- (1) question each	YES-during Screening	YES-during Study	NO
Dysphagia question	X		
atopic dermatitis (patients with AD only)			
asthma (patients with asthma only)			

*For each medical history condition of AD or asthma that you have, you will receive 1 "Additional Question" daily. During the screening period you will receive the Dysphagia question and this will continue during the study if you have symptoms of dysphagia (trouble swallowing).

As noted above, the "Additional Question(s)" will only populate AFTER you have completed the daily EG/EoD PRO Questionnaire. You must hit SEND & GO TO STARTPAGE to see all questionnaires.

START DIARY TODAY!

Additional Information regarding diary completion on Page 4!

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19.4 Appendix 4: ePRO Teaching Tool cont.

PROTOCOL AK002-016
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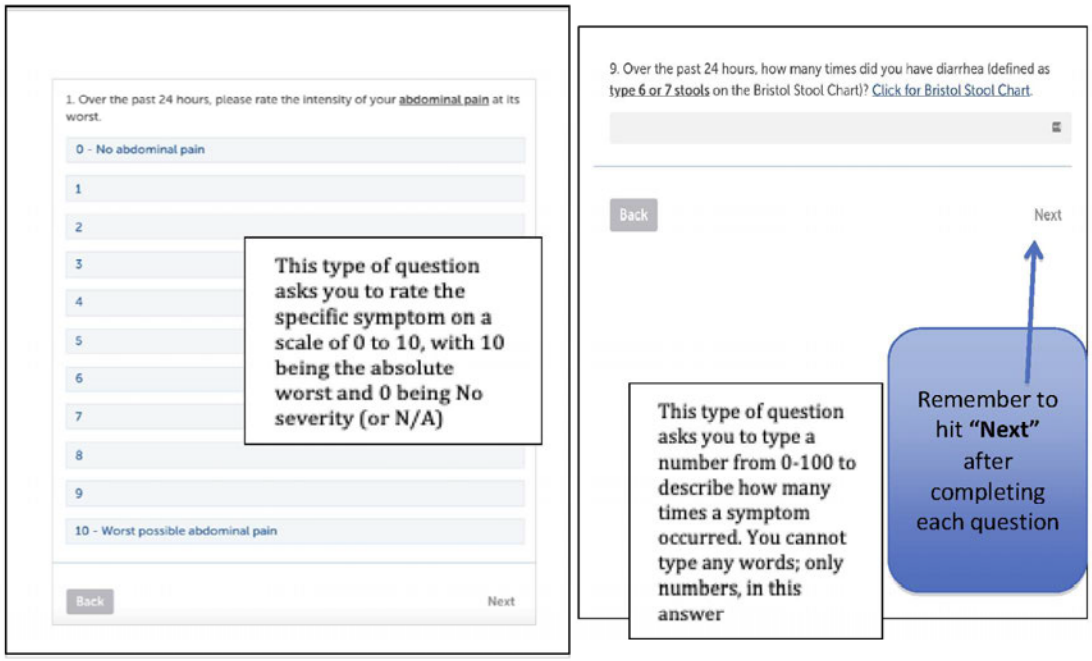
TYPES OF QUESTIONS ON EG/EoD QUESTIONNAIRE

There are 2 types of questions on the PRO Questionnaire, as shown below:



HOW TO ANSWER THE ViedocME QUESTIONS

- Each daily questionnaire should describe only the past 24 hours (1 day).
- If a questionnaire is missed do not try to answer information relating to events that happened more than 24 hours ago.
- You cannot skip any questions, answer each question the best that you can.
- If you make a mistake but have submitted the questionnaire, notify your study coordinator.

EXAMPLE:

- Diary is completed at 9:00PM on Wednesday night (Wednesday night's diary) for symptoms from 9PM Tuesday night-8:59PM on Wednesday night
- Vomiting occurs from 9-10PM Wednesday night
- Vomiting will be captured on next day's diary (Thursday night's diary)

WHAT TO DO IF YOU WILL BE WITHOUT INTERNET ACCESS

- Inform the Study Coordinator beforehand so that they can provide you with paper copies of the questionnaire(s). Use one copy of the questionnaire for each day you are without internet access.
- Only complete the questionnaire within 24 hours of the symptoms you are reporting. Do not try to remember more than 1 day (24 hours) in the past. Complete the paper questionnaire at the same time of the day you were completing the electronic questionnaire. Give all completed questionnaires to study coordinator as soon as possible.

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19.5 Appendix 5: Additional Questions

PID: _____

Date: _____

ADDITIONAL QUESTION(S)

Instructions: This questionnaire asks about symptoms that people with your condition may have**. Think of the last 24 hours** and choose the number that best **describes the intensity of your symptoms during that time.** *Please complete the daily questionnaire every day, at approximately the same time.*

Please choose an answer by selecting only one box for each question below, as appropriate.

Question # 1 Answer only if you have a history of 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 this question unless instructed to stop	Over the past 24 hours please rate the severity of difficulty **swallowing (dysphagia)** at its worst. ☐ 0 – No swallowing difficulty ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 – Worst possible swallowing difficulty

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19.6 Appendix 6: EGD Histology Directions

Details for collecting, labeling, and shipping specimens will be provided separately in the Central Histology Manual.

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 the subject has a history of concomitant EoE, if esophagus looks suspicious for EoE or if patient is symptomatic on dysphagia question)
  - 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.

The following will be reported for esophageal biopsies:

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

19.6 Appendix 6: EGD Histology Directions cont.

The following histopathologic parameters will be graded from 0 (absent) to 3 (marked or severe):

- 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/100 enterocytes when count is >20)
- Villous architecture

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

19.7 Appendix 7: 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)