A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AK002 in Patients with Moderately to Severely Active Eosinophilic Duodenitis who have an Inadequate Response with, Lost Response to, or were Intolerant to Standard Therapies

NCT Number: NCT04856891
IRB Approval Date: 13 Jul 2022
Document Date: 16 Jun 2022

825 Industrial Road, Suite 500, San Carlos, CA 94070

Clinical Research Protocol AK002-021

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AK002 in Patients with Moderately to Severely Active Eosinophilic Duodenitis who have an Inadequate Response with, Lost Response to, or were Intolerant to Standard Therapies

Protocol Number	AK002-021	
Version and Date	Original:	06 January 2021
	Amendment 1:	07 July 2021
	Amendment 2:	**16 June 2022**
Investigational Product	AK002 (lirentelimab)	
Study Phase	3	
Sponsor	Allakos Inc. 825 Industrial Road, Suite 500, San Carlos, CA 94070 USA	
Primary Medical Monitor	Name: Telephone: Email:	PPD MD PPD PPD
Backup Medical Monitor	Name: Telephone: Email:	PPD MD PPD PPD

Approval: PPD

16-Jun-2022 | 09:38 PDT

PPD MD, MBA
PPD

Date

Confidentiality Statement

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

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.

Protocol Number: AK002-021

IND: 135158

NCT ID: 04856891

Protocol Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AK002 in Patients with Moderately to Severely Active Eosinophilic Duodenitis Who Have an Inadequate Response with, Lost Response to, or Were Intolerant to Standard Therapies

Original Protocol: 06 January 2021

Amendment 1: 07 July 2021

Amendment 2: 16 June 2022

Investigator Printed Name: _____

Investigator Signature: _____

Date: _____

Table of Contents

List of Figures

List of Tables

List of Abbreviations

AC	Allergic conjunctivitis
ADA	Anti-drug-antibody
ADCC	Antibody-dependent cellular cytotoxicity
ADL	Activities of daily living
AE	Adverse event(s)
AESI	Adverse event(s) of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
anti-HBc	hepatitis B core antibody
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body mass index
CBC	Complete blood count
CFR	Code of Federal Regulation
CI	Confidence interval(s)
cm	Centimeter
CMH	Cochran-Mantel-Haenszel (test)
COVID-19	Coronavirus disease 2019
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CU	Chronic urticaria
eCDF	Empirical cumulative distribution function
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture system
EG	Eosinophilic gastritis
EGD	Esophago-gastro-duodenoscopy
EGE	Eosinophilic gastroenteritis
EGID	Eosinophilic gastrointestinal disorders
EGPA	Eosinophilic granulomatosis with polyangiitis
ELISA	Enzyme-linked immunosorbent assay
EoD	Eosinophilic duodenitis (formerly referred to as eosinophilic gastroenteritis)

EoE	Eosinophilic esophagitis
ET	Early Termination
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
H. pylori	*Helicobacter pylori*
HBsAG	Hepatis B surface antigen
hCG	Human Chorionic Gonadotropin
HEENT	Head, eyes, ears, nose, and throat
HES	Hypereosinophilic syndrome
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
hpf	High-power field
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Conference on Harmonisation
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IgG1	Immunoglobulin G1
IND	Investigational New Drug (application)
IP	Investigational product
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
IRT	Interactive Response Technology
ISM	Indolent systemic mastocytosis

ITIM	Immunoreceptor tyrosine-based inhibitory motif
ITT	Intent to treat
IUD	Intrauterine device
IV	Intravenous
kg	Kilogram
KR2	Kenward-Rodger's method
LARC	Long-acting reversible contraceptives
LLN	Lower limit of normal
LSM	Least square mean(s)
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Multiple imputation
MIU	Milli-international units
mL	Milliliter
mM	Millimolar
MMRM	Mixed model for repeated measures
MNAR	Missing not at random
MTD	Maximum tolerated dose
NaCl	Sodium chloride
NCI	National Cancer Institute
NCS	Not clinically significant
NCT	National Clinical Trial (Identifier)
NOAEL	No-observed-adverse-effect level
O&P	Ova and parasite (test)
OLE	Open-label extension
PCS	Physical component score
PD	Pharmacodynamics
PDF	Probability distribution function
PEF	Peak expiratory flow
CCI	[redacted]
CCI	[redacted]
PID	Patient identification number

PK	Pharmacokinetic(s)
PP	Per Protocol
PPI	Proton pump inhibitor
PRO	Patient reported outcome
SAE	Serious adverse event(s)
SAP	Statistical Analysis Plan
SE	Standard error(s)
CCI	[redacted]
Siglec	Sialic acid-binding, immunoglobulin-like lectin
SOC	System organ class
SOP	Standard operating procedure(s)
TEAE	Treatment-emergent adverse event(s)
TEAESI	Treatment-emergent adverse event(s) of special interest
TNF	Tumor necrosis factor
TSS	Total symptom score
TSS8	Total Symptom Score on 8 items
ULN	Upper limit of normal
USP	United States Pharmacopeia
WHODD	World Health Organization Drug Dictionary
WOCBP	Women of childbearing potential
w/v	Weight/volume

1. Protocol Synopsis

Study Title:	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AK002 in Patients with Moderate to Severe Active Eosinophilic Duodenitis who have an Inadequate Response with, Lost Response to, or were Intolerant to Standard Therapies
Sponsor:	Allakos Inc, 825 Industrial Road, Suite 500, San Carlos, CA 94070 USA
Number of Sites:	Approximately 35 clinical centers in the United States.

Nonclinical Background

AK002 is a humanized non-fucosylated immunoglobulin G1 (IgG1) monoclonal antibody directed against Siglec-8, a member of the CD33-related family of sialic acid-binding, immunoglobulin-like lectins (Siglecs).

Siglec-8 has a restricted tissue distribution, expressed selectively on the surface of mature eosinophils and mast cells, but not in early precursors of these cell populations. 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, over 700 healthy volunteers and patients with ISM, CU, severe AC, EG/EoD, eosinophilic esophagitis (EoE), and mast cell gastritis have received AK002 in clinical studies. In general, AK002 has been well tolerated. The most common treatment-emergent adverse events (TEAE) observed were infusion-related reactions (IRR). Most IRR were mild to moderate and many resolved on their own with no additional treatment required. IRR that were deemed more serious typically resolved within 24 hours, and additional corticosteroids and/or antihistamines were used in cases when slowing the rate of infusion and additional supportive care alone did not resolve the issue. Transient lymphopenia was observed after infusion of AK002 but was not associated with any clinical consequence, and lymphocytes recovered within 24 hours. A sustained depletion of eosinophils was observed that is consistent with the mechanism of action of AK002.

In the randomized, double-blind, placebo-controlled, Phase 2 study of AK002 in 65 patients with EG and/or EoD, patients were randomized to receive monthly doses of placebo, low dose AK002 (0.3, 1, 1, and 1 mg/kg), or high dose AK002 (0.3, 1, 3, and 3 mg/kg) in a 1:1:1 ratio (Dellon, 2020).

Clinical Background cont.

All primary and secondary endpoints were met in the study. There was a 97% and 92% mean reduction in eosinophils in the stomach/duodenum at the high dose and low dose, respectively, vs 10% increase for patients on placebo ($p<0.0001$).

There was also a statistically significant reduction in total symptom score on 8 items (TSS8) of 58% in the high dose group and 49% in the low dose group vs 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 Total Symptom Score (TSS) and >75% reduction from baseline in tissue eosinophils) vs 5% of placebo treated patients ($p<0.0001$) (Dellon, 2020).

Among the 65 patients, there were patients with EG without EoD, patients with EoD without EG, and patients with both EG and EoD, and these subgroups had similar symptoms and symptom severity. The treatment benefit of AK002 was observed across all of the subgroups, whether eosinophilia was reported in the duodenum with or without concomitant EG.

Patients with EoD without EG had similar histologic response on AK002 treatment as those with EG with or without EoD (All EG). AK002 treatment resulted in a -99.5% and -91.5% mean change in tissue eosinophils in patients with EoD and in patients with EG ± EoD, respectively. The proportion of patients achieving ≤1 eosinophil/high-power field (hpf) at the end of treatment was also similar (93.3% of EoD and 75% of EG ± EoD , respectively), compared to no patients on placebo. Additionally, symptomatic improvement was similar; EoD patients had a mean change in TSS of -57.4%, and EG ± EoD patients experienced a -51% mean change in TSS.

Among patients with concomitant eosinophilic esophagitis (EoE) in this study, a mean reduction of 95% of eosinophils/hpf in esophageal biopsies for AK002 was observed vs no change for placebo. Also, 13 of 14 AK002-treated patients (93%) were histologic responders as defined by ≤6 eosinophils/hpf vs 1 of 9 placebo-treated patients (11%). Dysphagia improved by 53% in AK002-treated patients vs 17% in placebo-treated patients.

More than 90% of patients in the Phase 2 study elected to continue into an open-label, long-term extension study (AK002-003X). In that study, a starting dose of 1 mg/kg AK002 was followed by doses of 3 mg/kg AK002. Premedication of 80 mg oral prednisone was administered the day before the first and second doses. Using this premedication regimen in the extension study, no IRR were reported on the first infusion of AK002.

The proposed dose regimen of 6 total doses of 3 mg/kg AK002, administered every 4 weeks, is based on experience with AK002 in healthy volunteers and in patients with ISM, CU, severe AC, mast cell disease, EoE, and EG/EoD.

The proposed dose of 3 mg/kg is based on experience across multiple prior studies, in which subjects received 60 mg prednisone as premedication followed by a dose of 3 mg/kg AK002 for the first infusion. This dosing regimen was well tolerated. By using this premedication regimen, the incidence and severity of IRR were substantially reduced.

Target Disease Background and Rationale

EoD represents a type of eosinophilic gastrointestinal disorder (EGID) that is characterized by chronic, often severe inflammation due to patchy or diffuse infiltration of eosinophils into layers of the duodenum (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 duodenum ± the stomach 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 (EGE) or eosinophilic enteritis although eosinophilic duodenitis (EoD) is more appropriate.

The gastrointestinal symptoms are believed to be due to the release of inflammatory mediators from activated eosinophils. However, emerging evidence suggests that activated mast cells also contribute to disease. Symptoms that are often debilitating commonly include abdominal pain, nausea, bloating, early satiety, loss of appetite, abdominal cramping, vomiting, diarrhea, and weight loss (Alhmoud, 2016; Lopez-Medina, 2015; Mansoor, 2017; Reed, 2015).

Jensen (2016) estimated the prevalence of EG and EoD to be 6.3/100,000 and 8.4/100,000, respectively (for patients from 1 to 64 years of age). Mansoor (2017) estimated the overall prevalence of EG to be 5.1/100,000 persons, though emerging evidence suggests that true prevalence is higher (Licari, 2020). More recently, a prevalence study was conducted in which 556 patients with chronic (≥6 months) gastrointestinal (GI) symptoms, unresponsive to pharmacologic/dietary interventions, and/or a historical diagnosis of irritable bowel syndrome or functional dyspepsia were screened. Four hundred five patients met symptom-severity criteria and were evaluated by EGD with standardized collection of biopsies for histopathology evaluation. Of those enrolled, 181 (45%) met histologic criteria for EG and/or EoD, and of the 181 patients, 122 (67%) were EoD-only patients (AK002-019 data on file).

There are no FDA-approved treatments for EoD. Current therapies and disease management include 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 EoD despite reports of providing partial benefit in some patients with EoE (Katz, 2013). Restricted/elemental diets are not effective long-term treatment as they require strict compliance and, in the case of elemental diets, are expensive and are often not reimbursed by insurance. In addition, compliance is poor and patient quality of life is greatly impacted (Bedell, 2018; Peterson, 2013; Wechsler, 2014). Corticosteroids, systemic or topical, 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, behavioral issues, weight gain, diabetes/glucose intolerance, and hypertension.

By markedly reducing the number of blood and tissue eosinophils and inhibiting the activation of mast cells, AK002 can be useful in the treatment of patients with 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 this chronic and debilitating disease, better treatment options are clearly needed.

Rationale for Dose Selection

The proposed dose regimen of 6 total doses of 3 mg/kg AK002, administered every 4 weeks is based on experience with AK002 in healthy volunteers and in patients with ISM, CU, severe AC, mast cell disease, EoE, and EG/EoD.

The proposed dose of 3 mg/kg AK002 is based on experience across multiple prior studies, in which subjects received 60 mg of prednisone as premedication, followed by a dose of 3 mg/kg AK002 for the first infusion. This dosing regimen was well tolerated. By using this premedication regimen, the incidence and severity of IRR were substantially reduced.

CCI

Number of Patients

Approximately 80 patients with moderately to severely active EoD (without EG) will be randomized 1:1 to receive 1 of 2 treatment regimens in a double-blind fashion:

- 6 doses of placebo every 4 weeks.
- 6 doses of AK002 at 3 mg/kg administered every 4 weeks.

All patients will receive 80 mg prednisone the day before the first infusion. The rationale for the number of patients is described under Statistical Analysis.

Study Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of AK002 in patients with EoD who have an inadequate response with, lost response to, or were intolerant to standard therapies.

Patients enrolled in the study will receive 6 infusions of placebo or AK002 administered every 4 weeks and will be followed for 12 weeks after last dose. Patients who elect to enter the optional long-term extension (OLE) period of the study will be followed for 5 weeks under the double-blind period of the study before entering the OLE period of the study.

Study Design cont.

Patients will be consented and then screened for up to 45 days prior to Day 1. Patients who meet all eligibility criteria can be enrolled into the study. Patients who do not meet all eligibility criteria at screening, or who qualify at screening but are not enrolled, may be assigned a new patient identification number and rescreened once. Patients rescreened within 30 days of signing the initial consent will not need to sign a new informed consent form (ICF) if no changes have been made to the ICF.

Patients will undergo an EGD and colonoscopy with biopsy at screening and again 4 weeks after last dose. For patients with a history of EoE and/or with a score of ≥3 on the dysphagia question during screening, esophageal biopsies will also be collected at screening and postdose. Biopsies from the gastric mucosa, duodenum, colon, and esophagus (as applicable) will be taken and reviewed by a central pathology reader. Additional biopsies will be collected for exploratory analysis.

The study is designed as follows:

- A screening period of 21–45 days with baseline evaluations for study eligibility, including active symptoms of disease (gathered by the patient reported outcome [PRO] questionnaire completed during screening) and EGD and colonoscopy with biopsy.
- Stool antigen test for *Helicobacter pylori* (*H. pylori*) will be assessed during screening to confirm no active *H. pylori* infection exists. If *H. pylori* is detected in tissue biopsies by the central pathologist, the patient should be excluded from the study.
- Prior EGD and colonoscopy biopsy samples may be used for eligibility as long as they were performed within 45 days of the AK002-021 screening window for the AK002-021 study and were performed and centrally assessed using the same criteria as for AK002-021 study.
- If patients meet histology and symptom eligibility criteria, they will be randomized and stratified by the highest weekly TSS of disease activity recorded during the screening period (<28 or ≥28 strata). The interactive response technology system (IRT) will assign patients 1:1 to receive 6 doses of placebo or AK002.
- Electronic PRO scores from the day before and day of colonoscopy will be excluded from the TSS since the bowel prep could artificially increase the scores.
- Prestudy medications and dietary restrictions should remain unchanged throughout the screening period and throughout the study. Systemic or topical corticosteroids above 10 mg prednisone daily (or the equivalent thereof) will not be allowed, except as a premedication prior to the first infusion only, or to treat an IRR that occurs during infusion, or for unforeseen circumstances when it is deemed to be medically necessary to treat an unrelated medical condition.
- Eligible patients will receive the first dose of placebo or AK002 (3 mg/kg) on Day 1 with premedication of 80 mg oral prednisone 12–24 hours prior to the start of the infusion.
- If the study drug is well tolerated (no stopping rules being met), patients will receive additional doses of placebo or AK002 (3 mg/kg) on Days 29, 57, 85, 113, and 141. With the exception of Day 1, steroid premedication will only be allowed with the written approval of the Medical Monitor.

Study Design cont.

- Patients will remain at the site for at least 1 hour of observation following the end of the infusion.
- An EGD and colonoscopy with biopsy will be performed on Day 169 (±3) or 28 (±3) days after the last dose of study drug if the patient terminates early from the study.
- Daily administration of the PRO questionnaire for all patients.
- Patients will rate their impression of disease severity CCI and disease improvement CCI at specified time points during the study.
- Patients will be prompted to answer additional questions about dysphagia and constipation on a daily basis during screening and throughout the study. These will be completed following the PRO questionnaire.
- Follow-up will occur for 84 (±3) days after last dose of study drug unless patients decide to enter the long-term OLE period of the study. Follow-up visits for patients opting not to enter the OLE period of the study will occur on Day 176 (±3), Day 197 (±3), and Day 225 (±3).
- Patients who receive all 6 doses of study drug have the option to receive AK002 by entering into the OLE period of the study if all eligibility criteria for the OLE period are satisfied. Patients who enter into the OLE period of the study may begin the extension dosing 1 day after completing the Day 176 visit of this protocol. Open-label extension patients will not complete the Day 197 or Day 225 procedures under the double-blind period of the study.
- Eligible patients who choose to participate in the OLE period will begin following the OLE Schedule of Assessments (Table 8 in Appendix 13) and may receive the first dose of open-label AK002 after the Day 176 visit in the double-blind period of the study has occurred.
- The subject will follow the visits and procedures of the double-blind period of the study until starting the OLE period of the study.
- Total study duration is approximately 35–37 weeks. For patients entering the OLE period of the study, the total study duration will be an additional 28–30 weeks.

Primary Objectives

To evaluate the efficacy and safety of 6 doses of AK002 in patients with moderate to severe EoD when compared with placebo. Efficacy will be evaluated by the following co-primary endpoints:

1) Proportion of tissue eosinophil responders at Week 24. A responder is a patient achieving a mean duodenal eosinophil count ≤15 cells/hpf in 3 highest duodenal hpf.

2) Change in TSS from baseline to Weeks 23–24 as measured by the Patient Reported Outcome (PRO) questionnaire.

The PRO TSS is comprised of the following 6 symptoms:

Primary Objectives cont.

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

Safety will be evaluated by AE reporting, laboratory safety tests, changes in vital signs, changes in concomitant medication use due to AE, immunogenicity, and other safety parameters.

Secondary Objectives

To further characterize the efficacy of AK002 in patients with EoD as measured by:

- Percent change in tissue eosinophils from baseline to Week 24.
- Proportion of patients achieving mean eosinophil count of ≤1 cell/hpf in 3 highest duodenal hpf at Week 24.
- Proportion of treatment responders at Weeks 23–24. A responder is defined as >30% improvement in TSS and mean eosinophil count ≤15 cells/hpf in 3 highest duodenal hpf.
- Proportion of patients who show ≥50% reduction in TSS from baseline to Weeks 23–24.
- Proportion of patients who show ≥70% reduction in TSS from baseline to Weeks 23–24.
- Percent change in weekly TSS over time.

Exploratory Objectives

To evaluate the effect of AK002 by comparing AK002 to placebo treatment for the following parameters:

- Change from baseline in CCI [redacted] over time.
- Changes in CCI [redacted] from baseline compared to post-treatment in the CCI [redacted] will be noted.
- Change from baseline in CCI [redacted] over time.
- Change from baseline in CCI [redacted] over time.

Study Population

Approximately 80 adult male and female patients with moderately to severely active EoD without EG with inadequate or loss of response to, or intolerance to standard therapies.

Patient Selection Criteria

Inclusion Criteria

Patients are eligible to enroll in the study if all of the following criteria are met:

Patient Selection Criteria – Inclusion Criteria cont.

1) Provide written informed consent.
2) Male or female aged ≥18 and ≤80 years at the time of signing the informed consent for entry.
3) Baseline endoscopic biopsy with ≥30 eosinophils/hpf in at least 3 hpf in the duodenum as determined by central histology assessment of biopsies collected during the screening EGD without any other significant cause for the eosinophilia.
4) Completion of at least 4 daily PRO questionnaires per week for a minimum of 3 weeks during screening.
5) A weekly average score of abdominal pain, nausea, or diarrhea ≥3 on the PRO questionnaire (score from 0–10) for at least 2 weeks of screening and a weekly average TSS of ≥10 for at least 2 weeks of screening.
6) Patients with inadequate or loss of response to, or who were intolerant to standard therapies for EoD symptoms, which could include PPI, antihistamines, systemic or topical corticosteroids, and/or diet, among others.
7) If patient is on preexisting dietary restrictions, willingness to maintain dietary restrictions throughout the study.
8) Willing and able to comply with all study procedures and visit schedule including follow-up visits.
9) Female patients must be either post-menopausal for at least 1 year with FSH level >30 MIU/mL at screening or surgically sterile (tubal ligation, partial or total 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, have a partner who had a vasectomy, or agree to abstain from sexual activity from screening until the end of the study or for 120 days following last dose of study drug, whichever is longer.

   Non-vasectomized male patients with female partners of childbearing potential must agree to either abstain from sexual activity or agree to use a highly effective method of contraception from screening until the end of the study or for 120 days following 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 (e.g., missed or later menstrual period) at any time during study participation.

Exclusion Criteria

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

1) Use of systemic or topical corticosteroids exceeding the equivalent of 10 mg/day of prednisone within 4 weeks prior to the screening visit.
2) Baseline endoscopic biopsy with ≥30 eosinophils/hpf in 5 hpf in the gastric mucosa, as determined by central histology assessment of biopsies collected during the screening EGD.
3) Change in the dose of corticosteroids (systemic or topical), PPI, leukotrienes, or diet therapy within 4 weeks prior to the screening visit.

Patient Selection Criteria – Exclusion Criteria cont.

4) Treatment with any immunosuppressive or immunomodulatory drugs that may interfere with the study within 12 weeks prior to the screening visit.
5) Prior exposure to AK002 or known hypersensitivity to any constituent of the study drug.
6) Active *H. pylori* infection as confirmed by stool antigen test for *H. pylo*ri.
7) History of inflammatory bowel disease, other chronic inflammatory diseases in the colon (with the exception of eosinophilic colitis), celiac disease, achalasia, or esophageal surgery.
8) History of bleeding disorders and/or esophageal varices considered to be clinically significant by the Investigator.
9) Other significant causes of gastric and/or duodenal eosinophilia or eosinophilic granulomatosis with polyangiitis (EGPA).
10) Confirmed diagnosis of hypereosinophilic syndrome (HES).
11) Women who are pregnant, breastfeeding, or planning to become pregnant while participating in the study.
12) Presence of an abnormal laboratory value considered to be clinically significant by the Investigator.
13) Any disease, condition (medical or surgical), or cardiac abnormality, which, in the opinion of the Investigator, would place the patient at increased risk.
14) History of malignancy, except carcinoma in situ, early-stage prostate cancer, or non-melanoma skin cancers. However, patients with cancers that have been in remission for more than 5 years and are considered cured can be enrolled.
15) Treatment for a clinically significant helminthic parasitic infection within 6 months of screening.
16) Positive helminthic infection on ova and parasite (O&P) test.
17) Seropositive for Strongyloides stercoralis at screening.
18) Seropositive for HIV or hepatitis at screening, except for vaccinated patients or patients with past but resolved hepatitis, at screening. See Appendix 12 for details on Hepatitis B and Hepatitis C serologic testing.
19) Vaccination with live attenuated vaccines within 30 days prior to initiation of treatment in the study, during the treatment period, or vaccination expected within 5 half-lives (4 months) of study drug administration. This exclusion criterion does not apply to all types and formulations of vaccines authorized by FDA or other regulatory authority for the prevention of COVID-19, which may be administered before, during, or after the 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.
20) Participation in a concurrent interventional study with the last intervention occurring within 30 days prior to study drug administration or 90 days or 5 half-lives, whichever is longer, for biologic products.

Patient Selection Criteria – Exclusion Criteria cont.

21) Known history of alcohol, drug, or other substance abuse or dependence that is considered by the Investigator to be ongoing and clinically significant.

22) Any other reason that in the opinion of the Investigator or the Medical Monitor makes the patient unsuitable for enrollment.

Test Product, Dose, and Administration

AK002 (CCI) and placebo are supplied as sterile liquids and will be diluted with 0.9% NaCl for intravenous infusion. The infusion will be administered as specified in the Pharmacy Manual.

AK002 and placebo are formulated in CCI pH 6.0, in Water for Injection (WFI).

Patients will self-administer 80 mg oral prednisone or an alternative premedication approved by the Allakos Medical Monitor 12–24 hours prior to the first infusion only. A steroid premedication prior to the start of the second through sixth infusions may only be administered with the prior written approval of the Medical Monitor.

AK002 at a dose of 3 mg/kg or placebo will be prepared according to the patient's body weight and administered on Day 1. Subsequent infusions of AK002 at a dose of 3 mg/kg or placebo according to the patient's body weight will be prepared on Day 29 (±3), Day 57 (±3), Day 85 (±3), Day 113 (±3), and Day 141 (±3).The initial infusion should be given over at least a 4-hour period, and the subsequent infusions should be given over at least a 1-hour period, depending on the patient's tolerance of the previous infusions and at the Investigator's discretion. Refer to the Pharmacy Manual for all infusion rates.

Any reduction in the infusion rate due to tolerability will not be considered a deviation from the protocol. All infusions must be completed within 8 hours of the study drug being mixed with NaCl.

Duration of Subject Participation

The total study duration for each patient will be approximately 8 months, which includes:

- A screening period of 21–45 days prior to study drug administration.
- A treatment period of 20 weeks.
- A follow-up period of 84 (±3) days after last dose of study drug.
- Patients who enter the OLE period of the study will participate in the double-blind period of Study AK002-021 for 26–32 weeks and will complete the study at least through the Day 176 visit.
- Patients who enter the OLE period prior to Day 197 will not complete the Day 197 visit or Day 225 visit of the double-blind study period but will instead follow the OLE schedule of events (Table 8) through Day 373.
- The patient will follow the visits and procedures of the double-blind period of the study until starting the OLE period of the study.

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 TEAE will be collected from the start of study drug administration through study completion or early termination (ET).

Severity will be assessed using the National Cancer Institute (NCI) 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 for clinical significance and relationship to study drug.

Additional safety evaluations include clinical laboratory tests comprising anti-drug antibody (ADA) to AK002, complete blood counts, chemistries and urinalyses, physical exams, and vital sign measurements.

The Medical Monitor will review safety data throughout the study. Certain safety data (post-treatment cell differentials as well as tissue eosinophil and mast cell counts) collected during the double-blind period of the study will not be provided to study sites or to the Sponsor as it may cause bias. The designated Safety Monitor will review blinded safety data as well as post-treatment cell counts and will escalate to the Medical Monitor, as needed, in a manner that does not cause bias.

An independent Data Monitoring Committee (iDMC) has been convened and will meet at regularly scheduled intervals in accordance with the iDMC charter.

Efficacy and Pharmacodynamic Evaluations

Daily self-administration of a disease-specific patient questionnaire, the Eosinophilic Gastritis/Duodenitis PRO (Appendix 1), will be used to evaluate signs and symptoms associated with EoD. Patient TSS will be evaluated, capturing the 6 common symptoms of 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. In addition to the PRO, patients will answer 1 daily question each about dysphagia and constipation.

Biopsies of the gastric, duodenal mucosa and colon collected during pre-treatment and post-treatment EGD and colonoscopy will be evaluated for number of eosinophils. In addition, the number of eosinophils in esophageal mucosa will be evaluated in patients with concomitant EoE. CCI [redacted] will be evaluated prior to each infusion and 1 hour (±15 minutes) after the end of each infusion.

Patients will be asked questions about the intensity of dysphagia and constipation daily, during screening and throughout the study. Patients will rate their quality of life using the non-disease-specific CCI (Appendix 2) at various study visits. Patients will rate their impression of disease severity CCI Appendix 8) and disease improvement CCI, Appendix 9) at specified time points during the study.

Pharmacokinetic and Anti-Drug-Antibody Evaluations

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 on Days 8, 15, 29, 57, 85, 113, 141, 169, 176, 197, and 225 or 28, 35, 56, and 84 (±3) days after last dose of study drug, if ET. On dosing days (Days 1, 29, 57, 85, 113, and 141), blood for PK will be collected predose.

Pharmacokinetic and Anti-Drug-Antibody Evaluations cont.

Blood (serum) will be collected for assessment of AK002 anti-drug antibodies (ADA) using a validated assay method. The ADA blood samples will be obtained at screening and predose on Days 1, 29, 57, 85, and 169, as well as on Day 225 or 84 (±3) days after last dose of study drug, if ET, and in the event of a suspected immunogenicity-related AE.

Sample Size Calculation

First Co-Primary Endpoint: A sample size of 40 patients per treatment group will have >90% power to demonstrate a greater proportion of histologic responders at Week 24 in AK002 patients when compared to placebo patients, assuming the proportions of histologic responders are 0.6 and 0.1 in the AK002 group and placebo group, respectively.

Second Co-Primary Endpoint: A sample size of 40 patients per treatment group will provide 80% power to detect a statistically significant difference of 7.4 points between AK002 and placebo in the mean reduction from baseline in TSS at Weeks 23–24, assuming a common standard deviation of 12.5 points (AK002-003 data on file).

Statistical Analysis

The primary efficacy analysis population is the Evaluable Population defined as all randomized patients who have received at least 1 infusion of study drug and at study entry do not meet any of the following criteria:

1) >6 eosinophils/hpf in at least 1 esophageal biopsy at baseline.
2) Documented history of irritable bowel syndrome and baseline diarrhea intensity ≥3.

The complement to the Evaluable population will be referred to as the Excluded population. It is worth remarking that for this study, if a patient has a history of concomitant EoE or if the esophagus looks suspicious for EoE or other condition, or if patient is symptomatic on screening dysphagia question, quantified by a score of >3 on the dysphagia question on at least 1 day during screening, then the following esophageal biopsies are collected during the baseline EGD:

- 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.

A count of >6 eosinophils/hpf in at least 1 esophageal site will be considered diagnostic for esophageal eosinophilia for the purposes of this study. In cases when there is a history of EoE, this could reflect active EoE although fulfillment of the diagnostic criteria for that condition may not be certain (see Appendix 5 for details).

The Per Protocol (PP) population is defined as Evaluable population patients who received at least 1 infusion of study drug and did not have significant protocol violations possibly interfering with assessment of efficacy.

Statistical Analysis cont.

The Safety population is defined as all patients who are randomized and have received at least 1 infusion of study drug.

The Evaluable and Excluded populations will be used for all efficacy analysis. The Per Protocol population will be used for the primary endpoints and select secondary endpoints analyses. The Safety population will be used for all safety analysis.

Patient disposition and reason for early discontinuation will be tabulated. Patient demographics, baseline characteristics, and treatment exposure will be summarized.

Efficacy Analysis: To evaluate the clinical benefit of AK002 in adult patients with active EoD when compared with placebo, efficacy endpoints will be co-primary.

The first co-primary endpoint will be analyzed using the Fisher's exact test. Patients who experience an intercurrent event (ICE), i.e., exit the study prematurely or initiate prohibited or restricted medications, prior to the end of Week 24 will be treated as non-responders. Proportion of responders and the associated 95% confidence interval (CI) will be presented for each treatment group. The between-group difference and the associated 95% CI will also be computed and presented.

Sensitivity analysis may be carried out using the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factor (baseline TSS <28 vs ≥ 28) to assess the robustness of Fisher's exact test results.

The second co-primary endpoint will be analyzed using mixed model for repeat measures (MMRM) with treatment, week, treatment-by-week interaction, and baseline TSS-by-week interaction as fixed factors, gender, and baseline TSS (continuous) as covariates, and study site (with pooling by geographic location) as random effect. If the model does not converge with pooled sites as a random effect, it will be simplified with pooled site as a fixed effect. Details about the method for pooling sites will be provided in the statistical analysis plan (SAP).

The weekly TSS is calculated as the average of the daily TSS. Weekly TSS will be set to missing if >3 daily TSS are missing. Baseline TSS will be the average of the last 2 weeks of daily TSS collected prior to the first infusion. The model variance-covariance matrix will be unstructured. However, if computation does not converge, the matrix will take the form of Toeplitz, autoregressive, or compound symmetry, whichever converges first.

Data on patients who experience an ICE, i.e., exit the study prematurely or initiate prohibited or restricted medications, prior to the end of Week 24 will be set to missing. If it is evident that the second co-primary endpoint is confounded by the influence of background variables, then the second co-primary analysis will be conducted adjusting for the effects of the background variables. Possible confounding factors may include age, presence of esophageal inflammation, history of IBS, and presence of diarrhea at baseline.

Statistical Analysis cont.

Two sensitivity analyses are planned. The first is a pattern-mixture model, where it will be assumed that AK002 subjects who experience an ICE will have a trajectory comparable to placebo post-ICE. This analysis will therefore provide a stress test of the missing at random (MAR) assumption of the MMRM employed in the principal analysis and will provide a conservative estimate of the treatment effect. The pattern-mixture model will be implemented using multiple imputations, and the inference of this sensitivity analysis will be based on the combined estimates using the standard multiple imputation technique. The imputed data sets will be analyzed with the same MMRM model utilized in the primary analysis and then summarized using PROC MIANALZE. The other is to analyze the average of Week 23 through Week 24 using ANCOVA with treatment and study site (with pooling by geographic location) as factors, gender and baseline TSS (continuous) as covariates. Missing Week 23 through Week 24 weekly TSS will be imputed prior to ANCOVA using SAS PROC MI under the MAR assumption. Detailed specifications for the missing data imputation will be provided in the SAP.

Analysis of binary secondary endpoints will be based on the CMH test stratified by the randomization stratification factor (baseline TSS <28 vs ≥28).

Change from baseline in continuous secondary outcomes measured at multiple post-baseline time points will be analyzed longitudinally using MMRM techniques. The model will include fixed effects for baseline value, treatment, week, treatment by week interaction, baseline value by week interaction, and allow for random subject effects. The model variance-covariance matrix will be unstructured. However, if computation does not converge, the matrix will take the form of Toeplitz, AR(1), and compound symmetry, whichever converges first. The Kenward-Rogers approach for computing denominator degrees of freedom will be used to account appropriately for pooling of within-subject and between-subject variance estimates. Least square means and the 95% CI for the between group difference will be estimated for each week.

To control for the overall false-positive error rate, the hypothesis testing for the primary and secondary endpoints using the Evaluable population in the subgroup defined above as the only population for primary inference are ordered as follows:

- The 2 co-primary efficacy endpoints will each be tested 2-sided at α=0.05 level. If both tests are statistically significant, the hypothesis tests for the secondary endpoints will proceed sequentially based on the order specified in Section 4.2.
- If at any point the statistical test is not significant at 2-sided α=0.05 level, the hypothesis testing procedure will stop. All endpoints prior to this point will be considered statistically significant, and inferential statistics after this point will be considered descriptive.

The estimand framework and the statistical methods will be further deliberated in the corresponding SAP as referenced to ICH Guidance E9 (R1) addendum (FDA, 2021), when appropriate.

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 (ITIM) 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 intravenous 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 intravenous administration of AK002 to transgenic mice was 100 mg/kg, which supports the Phase 1 studies in humans and is approximately 30 times the dose for this study, which is 3 mg/kg.

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, eosinophilic esophagitis (EoE), and eosinophilic gastritis (EG) and/or eosinophilic duodenitis (EoD), which was previously referred to as eosinophilic gastroenteritis (EGE).

Multiple doses of 3 mg/kg AK002 have been given to patients with ISM, CU, severe AC, mast cell gastritis, EoE, and EG and/or EoD. In these studies, patients reported improvements in disease symptoms with AK002 pharmacodynamic (PD) activity being observed for prolonged periods of time and AK002 pharmacokinetic (PK) parameters demonstrating a half-life amenable to administration every 4 weeks.

To date, over 700 healthy volunteers and patients with ISM, CU, severe AC, EG/EoD, EoE, and mast cell gastritis have been enrolled in clinical studies.

In general, AK002 has been well tolerated. The most common treatment-emergent adverse events (TEAE) observed were infusion-related reactions (IRR). Most IRR were mild to moderate, and many resolved on their own with no additional treatment required. IRR that were deemed more serious typically resolved within 24 hours, and additional corticosteroids and/or antihistamines were used in cases when slowing the rate of infusion and additional supportive care alone did not resolve the issue. Common symptoms of IRR were headache, nausea, sweating, flushing, and redness. Most IRR that occurred during the infusion could be managed by slowing or temporary interruption of the infusion, with minimal intervention. In 6 healthy volunteers who received 2 doses of 0.3 mg/kg, 4 weeks apart, the second dose was better tolerated than the first dose. This 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 in 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. 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, vs a 10% increase for placebo-treated patients ($p<0.0001$). There was also a statistically significant reduction in total symptom score (TSS) of 58% in the high dose AK002 group and 49% reduction in the low dose group AK002 vs a 24% reduction in the placebo group ($p=0.0012$ and $p=0.015$, respectively). Improvement in symptoms were 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) vs 5% of placebo-treated patients ($p<0.0001$) (Dellon, 2020).

Among the 65 patients, there were patients with EG without EoD, patients with EoD without EG, and patients with both EG and EoD, and these subgroups had similar symptoms and symptom severity. The treatment benefit of AK002 was observed across all of the subgroups, whether eosinophilia was reported in the duodenum with or without concomitant EG.

Patients with EoD without EG had a similar histologic response on AK002 treatment as those with EG with or without EoD (All EG). AK002 resulted in a -99.5% and -91.5% mean change in tissue eosinophils in patients with EoD without EG and in patients with EG ± EoD, respectively. The proportion of patients achieving ≤1 eosinophil/hpf at the end of treatment was also similar (93.3% and 75% of EoD without EG and All EG, respectively), compared to no patients on placebo. Additionally, symptomatic improvement was similar; EoD without EG patients had a mean change in TSS of -57.4%, and all EG patients experienced a -51% mean change in TSS.

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 vs no change for placebo-treated patients. Also, 13 of 14 AK002-treated patients (93%) were histologic responders as defined by ≤6 eosinophils/hpf vs 1 of 9 placebo-treated patients (11%). Dysphagia improved by 53% in AK002-treated patients vs 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 was used, followed by subsequent doses of 3 mg/kg. Premedication of 80 mg prednisone was administered the day before the first and second dose for 20 of the 58 patients dosed. Using this premedication regimen, no IRR were observed with the first infusion in the extension study.

Study AK002-016 was a Phase 3, randomized, double-blind, placebo-controlled study of lirentelimab in subjects with moderate-to-severe EG/EoD. The study enrolled 180 subjects with EG and/or EoD. Subjects were required to be moderately to severely symptomatic based on a patient reported symptom questionnaire and to have biopsy-confirmed eosinophilia of the stomach (≥30 eosinophils/hpf in 5 hpf) and/or duodenum (≥30 eosinophils/hpf in 3 hpf). Subjects were randomized 1:1 to receive a monthly infusion of placebo or 1 mg/kg lirentelimab IV for the first month followed by 5 doses of 3 mg/kg lirentelimab administered monthly. Disease symptoms were measured daily using a patient-reported outcome (PRO) questionnaire (TSS6) that scored 6 symptoms (abdominal pain, nausea, bloating, early satiety, abdominal cramping, and loss of appetite), each on a scale from 0 to 10. Co-primary endpoints were the proportion of responders with ≤4 eosinophils/hpf in 5 hpf in the stomach and/or ≤15 eosinophils/hpf in 3 hpf in the duodenum at the end of Week 24, and the absolute change from baseline in TSS6 at Weeks 23–24. Subjects who completed Study AK002-016 had the option to receive lirentelimab in Study AK002-016X, an open-label extension (OLE) study.

In this Phase 3 study, lirentelimab showed a statistically significant benefit compared to placebo on the histology co-primary endpoint but did not achieve statistical significance on the subject reported symptomatic co-primary endpoint (Table 1).

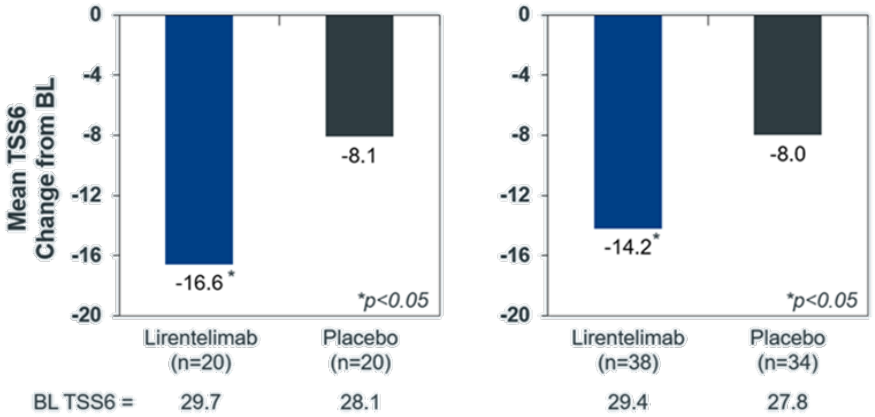
Table 1 Study AK002-016 in Subjects with Moderate-to-Severe EG/EoD: Co-Primary Endpoints of Histology and Symptoms

Co-Primary Endpoint	Lirentelimab (n=89)	Placebo (n=91)
Co-Primary Endpoint – Histology		
Histology Endpoint: Proportion of responders as determined by gastric or duodenal tissue eosinophil count[1]	84.6%	4.5%
p-value	<0.001	–
Co-Primary Endpoint – Symptoms		
Baseline TSS	29.5	27.57
Symptom Endpoint: Absolute mean change in subject reported TSS6[2]	-10.0	-11.5
p-value	0.343	–

1) A responder is a subject achieving the following peak eosinophil counts: eosinophil count ≤4 cells/hpf in 5 gastric hpf and/or eosinophil count ≤15 cells/hpf in 3 duodenal hpf. Endpoint assessed at end of Week 24.

2) TSS6 is a daily PRO questionnaire assessing 6 symptoms (abdominal pain, nausea, bloating, early satiety, abdominal cramping, and loss of appetite) on a scale from 0 to 10. Endpoint was assessed as mean change from baseline to Weeks 23–24.

When the change in TSS6 was analyzed for the Phase 3 AK002-016 study subjects enrolled at the sites that also participated in the Phase 2 AK002-003 study, the effect size as well as statistical significance for lirentelimab over placebo were consistent with the AK002-003 study (Figure 1). In contrast, when mean changes in TSS6 were analyzed separately for the Phase 3 AK002-016 sites who did not participate in the Phase 2 AK002-003 study, there was no separation between lirentelimab and placebo for subject symptom scores.



Left: Phase 2 Study AK002-003; Right: Phase 3 Study AK002-016 Sites that participated in AK002-003.
Least squares means and p-values derived from ANCOVA/MMRM models.

Figure 1 Effects Observed in Subjects at Clinical Sites that Participated in Both AK002-003 and AK002-016 Studies

The proposed dose regimen of 6 total doses of 3 mg/kg AK002, administered every 4 weeks, is based on experience with AK002 in healthy volunteers and in patients with ISM, CU, severe AC, mast cell disease, EoE, and EG/EoD. The proposed dose of 3 mg/kg is based on experience across multiple prior studies, in which subjects received 60 mg prednisone as premedication followed by a dose of 3 mg/kg AK002 for the first infusion. This dosing regimen was well tolerated. By using this premedication regimen, the incidence and severity of IRR were substantially reduced.

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).

EG and/or EoD 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 EoD is more accurate. The gastrointestinal symptoms are believed to be due to the release of inflammatory mediators from activated eosinophils, and also likely mast cells. Symptoms that are often 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 et al. (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 et al. (2017) estimated the overall prevalence of EG to be 5.1/100,000 persons, though emerging evidence suggests that true prevalence is higher (Licari, 2020).

More recently, a prevalence study was conducted in which 556 patients with chronic (≥6 months) gastrointestinal (GI) symptoms, unresponsive to pharmacologic/dietary interventions, and/or a historical diagnosis of irritable bowel syndrome or functional dyspepsia were screened. Four hundred five patients met symptom-severity criteria and were evaluated by EGD with standardized collection of biopsies for histopathology evaluation. Of those enrolled, 181 (45%) met histologic criteria for EG and/or EoD. Of the 181 patients, 122 (67%) were EOD-only patients (AK002-019 data on file).

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 poor, and patient quality of life is greatly impacted (Bedell, 2018; Peterson, 2013; Wechsler, 2014). Corticosteroids, systemic or topical (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, behavioral issues, weight gain, diabetes/glucose intolerance, and hypertension.

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 improvement in histology and symptom severity 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

The proposed dose regimen of 6 total doses of 3 mg/kg AK002, administered every 4 weeks, is based on experience with AK002 in healthy volunteers and in patients with ISM, CU, severe AC, mast cell disease, EoE, and EG/EoD.

Therefore, the proposed dosing regimen for this Phase 3 study with AK002 in patients with EoD without EG will be a starting dose of 3 mg/kg AK002 with 80 mg prednisone as a premedication prior to the first infusion only, followed by 5 doses of 3 mg/kg AK002 for subsequent infusions every 4 weeks.

4. Study Objectives

4.1 Primary Objective

To evaluate the efficacy and safety of 6 doses of AK002 in patients with moderate to severe EoD when compared with placebo.

Efficacy will be evaluated by the following co-primary endpoints:

1) Proportion of tissue eosinophil responders at Week 24, where a responder is a patient achieving a mean duodenal eosinophil count ≤15 cells/hpf in 3 highest duodenal hpf.
2) Change in TSS from baseline to Weeks 23–24 as measured by the PRO questionnaire.

The PRO TSS is comprised of the following 6 symptoms:

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

Safety will be evaluated by AE reporting, laboratory safety tests, changes in vital signs, changes in concomitant medication use due to AE, immunogenicity, and other safety parameters.

4.2 Secondary Objectives

To further characterize the efficacy of AK002 in patients with EoD as measured by:

- Percent change in tissue eosinophils from baseline to Week 24.
- Proportion of patients achieving mean eosinophil count of ≤1 cell/hpf in 3 highest duodenal hpf at Week 24.
- Proportion of treatment responders at Weeks 23–24. Responder is defined as >30% improvement in TSS and mean eosinophil count ≤15 cells/hpf in 3 highest duodenal hpf.
- Proportion of patients who show ≥50% reduction in TSS from baseline to Weeks 23–24.
- Proportion of patients who show ≥70% reduction in TSS from baseline to Weeks 23–24.
- Percent change in weekly TSS over time.

4.3 Exploratory Objectives

To evaluate the effect of AK002 by comparing AK002 to placebo treatment for the following parameters:

- Change from baseline in CCI [redacted] over time.
- Changes in CCI [redacted] from baseline compared to post-treatment in the CCI [redacted] will be noted.
- Change from baseline in CCI [redacted] over time.
- Change from baseline in CCI [redacted] over time.

4.4 Safety Objectives

To evaluate the safety and tolerability of AK002 by determining incidence and severity of AE, study withdrawals due to AE, changes in vital signs and laboratory tests including immunogenicity, changes in concomitant medication use due to AE, and other safety parameters.

4.5 Target of Estimation

The estimand (target of estimation) for Protocol AK002-021 is:

> *In patients with EoD, what is between group (AK002 vs. Placebo) difference in the proportion of tissue eosinophil responders at Week 24, and group difference in TSS from baseline to Weeks 23–24 as measured by the PRO questionnaire.*

Sections below describe the attributes of the estimand consistent with the ICH E9 Addendum (FDA, 2021).

4.5.1 Population Targeted by the Scientific Question

The population targeted by the scientific question is defined by the inclusion and exclusion criteria as part of the study protocol. Patients must have a histological diagnosis of EoD. A key aspect of eligibility is that subjects must have a weekly average score of abdominal pain, nausea, or diarrhea ≥3 on the PRO questionnaire (score from 0–10) for at least 2 weeks of screening and a weekly average TSS of ≥10 for at least 2 weeks of screening. It is noted that history of inflammatory bowel disease, other chronic inflammatory diseases in the colon (with the exception of eosinophilic colitis), celiac disease, achalasia, or esophageal surgery is an exclusionary measure in the study. Supplementary analysis of data from the AK002-016 study focused on identification of baseline characteristics, which correlate with degree of change in TSS6 at Weeks 23–24. This examination identified 8 variables (age, gender, duodenal eosinophil counts, diarrhea frequency, history of IBS, abdominal pain, >6 esophageal eosinophils/hpf, and history of IBS in combination with diarrhea intensity ≥3) that most influenced the degree of change of the TSS6 endpoint. Two of the variables (>6 esophageal eosinophils/hpf and history of IBS in combination with diarrhea intensity ≥3) potentially reflect other disease states (IBS, GERD, or even active EoE) that could potentially impact multiple symptom components of TSS6. To ensure these 2 variables do not compromise the capacity to detect the treatment effect with symptoms of EoD as measured by the TSS6 questionnaire, the primary comparison of AK002 vs placebo will be conducted only on the Evaluable population defined as patients who do not meet any of the following criteria:

1) >6 eosinophils/hpf in at least 1 esophageal site at baseline.

2) Documented history of irritable bowel syndrome and baseline diarrhea intensity ≥3.

4.5.2 Variables of Interest (or Endpoint) Required to Address the Scientific Question

The co-primary endpoints to be obtained for each subject in this study to address the scientific question are tissue eosinophil responders (as defined in Section 4.1) at Week 24 and change in TSS from baseline to Weeks 23–24 as measured by the PRO questionnaire.

4.5.3 Treatment

AK002 or placebo administered to subjects on Days 1, 29, 57, 85, 113, and 141.

4.5.4 Intercurrent Events

The events below are considered ICE confounding with the efficacy outcomes.

- Premature discontinuation from the study.
- Use of prohibited/restricted medication.

Further clarification and handling of ICE including prohibited/restricted medications will be detailed in the statistical analysis plan (SAP).

4.5.5 Strategy for Handling Intercurrent Events

For the analysis of the trial product estimand, tissue eosinophil values and TSS will be counted as non-responders for binary variables and set to missing for continuous outcomes from the point when an ICE occurs. An appropriate method for handling missing data through statistical modeling, e.g., multiple imputation (MI) will be used. The estimand will provide an answer to the question that is crucial to individual subjects, "If I take this study medication as part of my treatment regimen, without adding any further medications that may impact the underlying disease or exit the study prematurely, what improvements in histology and PRO symptoms might be anticipated after 24 weeks?"

5. Study Design

5.1 Study Overview

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of AK002 in patients with moderately to severely active EoD without EG who have an inadequate response with, lost response to, or were intolerant to standard therapies.

Patients enrolled in the study will receive 6 infusions of placebo or AK002 administered every 4 weeks and will be followed for 12 weeks after last dose unless patients elect to enter the optional open-label extension (OLE) period of the study.

Patients will be consented and then screened for 21–45 days prior to Day 1. Patients who meet all eligibility criteria can be enrolled into the study. Patients who do not meet all eligibility criteria at screening, or who qualify at screening but are not enrolled, may be assigned a new patient identification number and rescreened once. Patients rescreened within 30 days of signing the initial consent will not need to sign a new informed consent form (ICF) if no changes have been made to the ICF.

Patients will undergo EGD and colonoscopy with biopsy at screening and again 4 weeks after last dose. The EGD and colonoscopy should take place on the same day in order to minimize effects of procedure premedication on the PRO scores. For patients with a history of EoE and/or with a score of ≥3 on the dysphagia question on at least 1 day during screening, esophageal

biopsies will also be collected at screening and postdose. Biopsies from the gastric mucosa, duodenum, colon, and esophagus (as applicable) will be taken and reviewed by a central pathology reader. Additional biopsies will be collected for exploratory analysis.

The study is designed as follows:

- A screening period of 21–45 days with baseline evaluations for study eligibility, including active symptoms of disease (gathered by the patient reported outcome [PRO] questionnaire completed during screening) and EGD and colonoscopy (performed on the same day) with biopsy.
- Stool antigen test for *Helicobacter pylori* (*H. pylori*) will be assessed during screening to confirm no active *H. pylori* infection exists. If *H. pylori* is detected in tissue biopsies by the central pathologist, the patient should be excluded from the study.
- Prior EGD and colonoscopy biopsy samples may be used for eligibility as long as they were performed within 45 days of the screening window for the AK002-021 study and were performed and centrally assessed using the same criteria as for the AK002-021 study.
- If patients meet histology and symptom eligibility criteria, they will be randomized and stratified by the highest weekly mean TSS of disease activity recorded during the screening period (<28 or ≥28 strata). The IRT will assign patients 1:1 to receive 6 doses of AK002 or placebo.
- Pre-study medications and dietary restrictions should remain unchanged throughout the screening period and throughout the study. Systemic or topical corticosteroids above 10 mg prednisone daily (or the equivalent thereof) will not be allowed, except as a premedication prior to the first infusion only, 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.
- Eligible patients will receive the first dose of placebo or AK002 (3 mg/kg) on Day 1 with premedication of 80 mg oral prednisone 12–24 hours prior to the start of the infusion.
- If the study drug is well tolerated (no stopping rules being met), patients will receive additional doses of placebo or AK002 (3 mg/kg) on Days 29, 57, 85, 113, and 141. With the exception of Day 1, steroid premedication will only be allowed with the written approval of the Medical Monitor.
- Patients will remain at the site for at least 1 hour of observation following the end of the infusion.

- A repeat EGD and colonoscopy with biopsy will be performed on Day 169 (±3) or 28 (±3) days after last dose of study drug if patient early-terminates from the study (between the Day 29 visit and the Day 169 visit).
- Daily administration of the PRO questionnaire (including additional questions) throughout the study and the follow-up period for all patients.
- Patients will rate their impression of disease severity [redacted] and disease improvement [redacted] at specified time points during the study.
- Patients will be prompted to answer additional questions about dysphagia and constipation on a daily basis during screening and throughout the study. These will be completed following the PRO questionnaire.
- Follow-up will occur for 84 (±3) days after last dose of study drug unless patients decide to enter the long-term, open-label extension (OLE) period of the study. Follow-up visits for patients opting not to enter the OLE period of the study will occur on Day 176 (±3), Day 197 (±3), and Day 225 (±3).
- Patients who receive all 6 doses of study drug have the option to receive AK002 by entering into the OLE period of the study if all eligibility criteria for the OLE period are satisfied. Patients who enter into the OLE period of the study may begin the extension dosing 1 day after completing the Day 176 visit of this protocol. Open-label extension patients will not complete the Day 197 or Day 225 procedures under the double-blind period of the study.
- Eligible patients who choose to participate in the OLE period will begin following the OLE Schedule of Assessments (Table 8 in Appendix 13) after completing the Day 176 double-blind period procedures and will receive the first dose of open-label AK002 approximately 1 week after Day 169 (on Day 177).
- Total study duration is approximately 35–37 weeks. For patients entering into the OLE period of the study, the total study duration will be approximately an additional 28-30 weeks.

5.2 Schedule of Events

The overall schedule of procedures and assessments are described in Table 2.

Table 2 Study AK002-021 Schedule of Assessments: Double-Blind Period

Assessment Description	Screening (21–45 days)		Treatment Period (20 weeks)								Follow-Up Period[30] (12 weeks)			
	Baseline[1]	Prior to Day 1	Dose 1 Day 1[2]	Day 8 (±2 days)	Day 15 (±2 days)	Dose 2 Day 29 (±3 days)	Dose 3 Day 57 (±3 days)	Dose 4 Day 85 (±3 days)	Dose 5 Day 113 (±3 days)	Dose 6 Day 141 (±3 days)	Day 169 (±3 days) or 28 days after last dose if ET	Day 176 (±3 days) or 35 days after last dose if ET[29]	Day 197 (±3 days) or 56 days after last dose if ET[29]	Day 225 (±3 days) or 84 days after last dose if ET
Informed consent	X													
Demographics	X		X											
Medical History	X		X											
Prior and Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height[2]	X		X			X	X	X	X	X		X	X	X
Vital Signs[3]	X		X		X	X	X	X	X	X		X	X	X
10 or 12-lead ECG[4]	X													
Complete Physical Exam[5]	X													
Symptom-Directed Physical Exam[6]			X		X	X	X	X	X	X		X	X	X
Baseline Diet Assessment[7]	X													
Baseline Diet Compliance[8]			X		X	X	X	X	X	X		X	X	X
Previous Treatments and Procedure Review	X													
Stool for Ova and Parasite[9]	X													
Stool antigen test for *H. pylori*[32]	X													
ePRO Activation and Training[10]	X													
ePRO Questionnaire (will include Additional Questions)[11]	<---------- Complete electronically 1 time daily ---------->													
CCI	X		X			X	X	X	X	X		X	X	
CCI	<---------- Complete electronically on Screening Day 19, Study Day 7, Study Day 28, and Study Day 225 or ET ---------->													
CCI	<---------- Complete electronically on Study Day 7, Study Day 28 and Study Day 225 or ET ---------->													
EGD + colonoscopy with Biopsy[12,14]	X										X			

Table 2 Study AK002-021 Schedule of Assessments: Double-Blind Period cont.

Assessment Description	Screening (21–45 days)		Treatment Period (20 weeks)								Follow-Up Period[30] (12 weeks)			
	Baseline[1]	**Prior to Day 1**	**Dose 1 Day 1**[2]	**Day 8** (±2 days)	**Day 15** (±2 days)	**Dose 2 Day 29** (±3 days)	**Dose 3 Day 57** (±3 days)	**Dose 4 Day 85** (±3 days)	**Dose 5 Day 113** (±3 days)	**Dose 6 Day 141** (±3 days)	**Day 169** (±3 days) or 28 days after last dose if ET	**Day 176** (±3 days) or 35 days after last dose if ET[29]	**Day 197** (±3 days) or 56 days after last dose if ET[29]	**Day 225** (±3 days) or 84 days after last dose if ET
Blood for CBC with differential[21]	X		X	X	X	X	X	X	X	X	X	X	X	X
Blood for Chemistry[15,22] (Screening Chemistry includes hCG and FSH)	X		X	X	X	X	X	X	X	X	X	X	X	X
Blood for Serology and Strongyloides stercoralis [16]	X													
Blood for Total Serum IgE[17]	X											X		
Blood for PK[23]	X			X	X	X	X	X	X	X	X	X	X	X
Blood for ADA[24]	X		X			X	X	X			X			X
Urine for Urinalysis[25]	X					X								X[25]
Dipstick Pregnancy Test[26]			X			X	X	X	X	X		X	X	
Eligibility Assessment	X	X	X											
Premedication: Prednisone[19]		X												
Access IRT: Stratification and Randomization[18]			X											
Access IRT: IP Kit Assignment			X			X	X	X	X	X				
Study Drug Administration[20]			X			X	X	X	X	X				
Non-serious Adverse Events[27]			X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events[28]			X	X	X	X	X	X	X	X	X	X	X	X
Begin OLE period of the study at least 1 day after Day 176 Visit (if applicable)[29, 31]												X	Day 197 and Day 225 visits are not applicable for OLE patients	

Table 2 Notes

ADA:	Anti-AK002 antibody	ET:	Early Termination	IRT:	Interactive Response Technology
CBC:	Complete blood count	FSH:	Follicle-stimulating hormone	CCI	[redacted]
ECG:	Electrocardiogram	hCG:	Human Chorionic Gonadotropin	CCI	[redacted]
ePRO:	electronic Patient Reported Outcome	IP:	Investigational Product	PK:	Pharmacokinetics

1) Baseline screening visit can occur over several days within the screening period. Day 1 can begin as soon as eligibility criteria are met.

2) At screening, height (in cm) and weight (in kg) will be recorded. Body weight will also be measured on Days 1, 29, 57, 85, 113, 141, and on follow-up Days 176, 197 and 225 or 28,56, and 84 days after last dose, if ET. Current body weight or body weight from 1 day prior will be used to calculate the amount of AK002/placebo to be mixed with NaCl for the appropriate dose to be administered on each infusion day.

3) Vital signs will be measured at screening, Days 176, 197, and 225 or 28,56 and 84 days after last dose if ET and on all dosing days: within 30 minutes predose, 15 (±5) minutes after the start of study drug infusion, within 15 minutes following the end of infusion and just prior to discharge. Additional vital signs measurements may be collected at the Investigator's discretion if an IRR occurs. Vital signs including systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate will be measured after the patient has been at rest for ≥5 minutes and before any blood draws have been obtained (unless collected for an IRR).

4) A 10-lead or 12-lead ECG will be obtained at screening before any blood is drawn and after the patient has been in the appropriate position for ≥5 minutes.

5) A complete physical examination will be performed by either the Investigator or designee and include the following body system or organ assessments: skin; head, eyes, ears, nose and throat; thyroid; lungs; cardiovascular; abdomen; extremities; lymph nodes; and a brief neurological examination.

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

7) A baseline diet assessment (Appendix 3) will be performed using standardized questions. Eating patterns, food avoidance behaviors, and confirmed allergies will be captured.

8) A baseline diet compliance check will be performed at every study visit, except as noted above, and any variances from the baseline diet documented. Patients should maintain the baseline diet throughout the study.

9) Fecal collection kits for ova and parasite test will be provided to patients at screening. Collection kits should be returned to the clinical site within 1 day of collection. Negative results must be available prior to randomization.

10) Activate PRO questionnaire and provide patient with unique username and password. PRO questionnaire should be activated for all patients on screening Day 1.

11) PRO should be completed around the same time each day. Prior to enrollment, the PRO weekly averages of abdominal pain, nausea, and diarrhea over the screening period will be calculated and used to assess eligibility. Weekly average Total Symptom Score (TSS6) will be calculated for eligibility and stratification. Patients will also complete an additional question each about dysphagia and constipation daily during the screening period and throughout the study. The additional questions will be completed following the PRO questionnaire.

Table 2 Notes cont.

12) EGD + colonoscopy with biopsy (performed on the same day whenever possible) will include specimens from the gastric mucosa, duodenum, colon and esophagus (as applicable). Specimens will be processed by the central laboratory. See the Histology Manual for collection, processing, and shipping details. The specimens will be evaluated by a central pathology reader. Additional biopsies will be collected for exploratory analysis. Prior EGD and colonoscopy biopsy samples may be used for eligibility as long as they were performed within 45 days of the AK002-021 screening window for the AK002-021 study and were performed and centrally assessed using the same criteria as for the AK002-021 study, and there were no changes to EoD therapy following the EGD.

13) The CCI [redacted] is to be completed electronically by patient, in clinic, prior to any blood draw, physical exam, or vital sign measurements.

14) See Appendix 5 for biopsy assessments. The post-treatment EGD + colonoscopy and biopsy assessments will be performed on Day 169 (±3) or 28 (±3) days after last dose of study drug if ET. Post-treatment EGD + colonoscopy biopsy results will be blinded to the site.

15) Blood for baseline chemistry, including hCG and FSH, will be collected during the screening period. Only patients of childbearing potential and post-menopausal women are required to have hCG and FSH testing completed.

16) Blood for serology testing will be collected during screening and will include HBsAg, hepatitis C antibody, anti-HBc, and HIV, as well as Strongyloides stercoralis.

17) Blood samples for total serum IgE will be collected during screening and on Day 176 or 35 (±3) days after last dose of study drug, if ET.

18) Stratification based on TSS of <28 or ≥28 will occur. Randomization and stratification will be conducted through the IRT system.

19) Premedication with 80 mg oral prednisone or approved alternative is required 12–24 hours prior to the first infusion. Premedication prior to the start of the second through sixth infusions will only be administered with the prior written approval of the Medical Monitor.

20) Study drug will be administered as a single peripheral intravenous infusion over at least 4 hours for Dose 1 and at least 1 hour for subsequent doses. Refer to the Pharmacy Manual.

21) Blood for CBC with differential, including absolute blood eosinophil count, will be obtained once during screening, Day 8, Day 15, and once during each follow-up visit or ET visit, as well as twice during dosing days just prior to each infusion and 1 hour (±15 minutes) after the end of each infusion. All differential blood counts from Day 1 (postdose) through the end of the patient's participation will be blinded to the Sponsor and the site. An unscheduled CBC may be collected at the request of the Safety Monitor.

22) Blood for chemistry will be obtained once during screening and once during each follow-up visit or ET visit as well as predose on dosing days.

23) Blood for PK will be obtained predose on dosing Days 29, 57, 85, 113, and 141, as well as during screening and on Days 8, 15, 169, 176, 197, and 225 or 28, 35, 56, and 84 (±3) days after last dose of study drug if ET.

24) Blood for ADA will be collected at screening and predose on dosing Days 1, 29, 57, and 85, as well as on Days 169 and 225 or 28 and 84 (±3) days after last dose of study drug if ET. The ADA sample will also be collected any time an immunogenicity-related AE occurs.

25) Urine for standard urinalysis will be obtained at screening, predose on dosing Day 29, ET, and symptom based, as necessary.

Table 2 Notes cont.

26) Urine will be collected for dipstick pregnancy test on all infusion days and on Day 176 and Day 197 or 35 and 56 (±3) days after last dose of study drug, for all patients of childbearing potential. Test kits will be supplied by the central laboratory. Tests will be completed on site and evaluated prior to each infusion.

27) The capture of non-serious AE and AESI will begin after the first dose of study drug has occurred.

28) The reporting of SAE occurring after signing the informed consent and prior to the first infusion will be limited to those that relate to screening procedures. The capture of all SAE and AE that are not related to screening procedures will begin at the time of first infusion of study drug. For patients participating in the OLE period, AE will be assessed and recorded in the CRF of the AK002-021 double-blind treatment period database up until the start of the first open-label infusion, after the Day 176 visit. The AE will be recorded in the CRF of the AK002-021 OLE period database beginning with the start of the first open-label infusion after Day 176.

29) Patients who continue in the OLE period of the study will complete the procedures for Day 176 and may begin open-label dosing in the OLE period of the study, if eligible, 1 day after completion of the Day 176 visit. In this case, patients will not complete the Day 197 or Day 225 procedures under the double-blind period of the study.

30) The ET visits should be conducted 28, 35, 56, and 84 (±3) days after last dose of study drug or prior to this, if necessary, to ensure compliance with the visit. If only 1 ET visit is possible, EGD + colonoscopy and end-of-study procedures may occur on the same day. If the end-of-study visit occurs more than 35 days after last dose of study drug, then perform the visit as soon as possible. The procedures listed under the 28-day and 35-day post-study drug visit will be conducted unless otherwise directed by the Medical Monitor. For patients participating in the OLE period, AE and concomitant medications should be collected and recorded in the AK002-021 double-blind treatment period database up until the start of the first open-label infusion after the Day 176 visit. This includes prednisone premedication administered after the Day 176 visit of the OLE period, which should be recorded in the Concomitant Medications CRF of both the AK002-021 double-blind treatment period database and the AK002-021 OLE period database.

31) The final hematology assessment for the double-blind period of the study ***must*** be collected ***prior to*** the patient taking prednisone premedication for the first dose of the OLE period. Therefore, dosing in OLE must take place at least 1 day after completion of the Day 176.

32) Stool antigen test for *H. pylori* will be obtained to confirm that no existing active *H. pylori* infection is present. Fecal collection kits (same container as for ova and parasite testing) should be returned to the clinical site within 1 day of collection. Negative results must be available prior to randomization. If *H. pylori* is detected in tissue biopsies by the central pathologist, the patient should be excluded from the study. In case of a positive test, the patient must be screen-failed. After *H. pylori* treatment and an additional 6 weeks later, patient may be reconsented and will receive a new patient number.

6. Criteria for Evaluation

6.1 Safety Endpoints

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

- Adverse events (Section 13.1) including severity, withdrawals due to AE, and other safety parameters
- Adverse events of special interest (AESI), IRR, malignancy, and opportunistic infections (Section 13.3)
- Anti-drug antibodies (Section 11.5.4): Blood (serum) will be collected for assessment of ADA using a validated assay method. The ADA blood samples will be obtained at screening, predose on Days 1, 29, 57, 85, and additionally on Day 169 and Day 225 or 84 (±3) days after last dose, if ET.
- Blood chemistry (Section 11.5)
- Hematology (Section 11.2.5)
- Urinalysis (Section 11.5.2)
- Physical examination (Section 11.3.2 and Section 11.3.5)
- Changes in vital signs (Section 11.3.7)
- Changes in concomitant medication use due to AE (Section 11.3.1)

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 at screening, predose on Days 29, 57, 85, 113, and 141 and additionally on Days 8, 15, 169, 176, 197, and 225 or 28, 35, 56, and 84 (±3) days after last dose, if ET. AK002 concentrations in serum will be used to calculate AK002 exposure.

6.2.1 Primary Efficacy Endpoints

To evaluate the efficacy and safety of 6 doses of AK002 in patients with moderate to severe EoD when compared with placebo. Efficacy will be evaluated by the following co-primary endpoints:

1) Proportion of tissue eosinophil responders at Week 24. A responder is a patient achieving a mean duodenal eosinophil count ≤15 cells/hpf in 3 highest duodenal hpf.
2) Change in TSS from baseline to Weeks 23–24 as measured by the PRO questionnaire.

The PRO TSS is comprised of 6 symptoms, as listed below:

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

The severity and frequency of diarrhea and vomiting will also be collected on the PRO questionnaire but will not be included in the calculation of the TSS.

6.2.2 Secondary Efficacy Endpoints

To further characterize the efficacy of AK002 in patients with EoD as measured by:

- Change in tissue eosinophils from baseline to Week 24.
- Proportion of patients achieving mean eosinophil count ≤1 cell/hpf in 3 highest duodenal hpf at Week 24.
- Proportion of treatment responders at Weeks 23–24. A responder is defined as >30% improvement in TSS and mean eosinophil count ≤15 cells/hpf in 3 highest duodenal hpf.
- Proportion of patients who achieve ≥50% reduction in TSS from baseline to Weeks 23–24.
- Proportion of patients who achieve ≥70% reduction in TSS from baseline to Weeks 23–24.
- Change in weekly TSS over time.

6.2.3 Exploratory Efficacy Endpoints

To evaluate the effect of AK002 by comparing AK002 to placebo treatment for the following parameters:

- Change from baseline in CCI [redacted] over time.
- Changes in CCI [redacted] from baseline compared to post-treatment in the CCI [redacted] will be noted.
- Change from baseline in CCI [redacted] over time.
- Change from baseline in CCI [redacted] over time.

7. Patient Selection

7.1 Number of Patients

A total of approximately 80 patients will be dosed in the study in which 40 patients will receive 6 doses of 3 mg/kg AK002 and 40 patients will receive 6 doses of placebo every 4 weeks in a randomized, double-blind manner. All patients will be pretreated with 80 mg prednisone the day before the first infusion.

7.2 Number of Sites

Approximately 35 sites in the United States will participate in this study.

7.3 Study Population

Approximately 80 male and female patients with moderately to severely active EoD (without EG), aged ≥18 and ≤80 years, who fulfill the eligibility criteria specified below, will be enrolled into the study.

7.4 Inclusion Criteria

Patients are eligible to enroll in the study if all of the following criteria are met:

1) Provide written informed consent.
2) Male or female aged ≥18 and ≤80 years at the time of signing the informed consent for entry.
3) Baseline endoscopic biopsy with ≥30 eosinophils/hpf in at least 3 hpf in the duodenum as determined by central histology assessment of biopsies collected during the screening EGD without any other significant cause for the eosinophilia.
4) Completion of at least 4 daily PRO questionnaires per week for a minimum of 3 weeks during screening.
5) A weekly average score of abdominal pain, nausea, or diarrhea ≥3 on the PRO questionnaire (score from 0–10) for at least 2 weeks of screening and a weekly average TSS of ≥10 for at least 2 weeks of screening.
6) Inadequate or loss of response to, or intolerant to standard therapies for EoD symptoms, which could include PPI, antihistamines, systemic or topical corticosteroids, and/or diet, among others.
7) If patient is on pre-existing dietary restrictions, willingness to maintain dietary restrictions throughout the study.
8) Willing and able to comply with all study procedures and visit schedule including follow-up visits.

9) Female patients must be either post-menopausal for at least 1 year with FSH level >30 MIU/mL at screening or surgically sterile (tubal ligation, partial or total 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, have a partner who had a vasectomy, or agree to abstain from sexual activity from screening until the end of the study, or for 120 days following last dose of study drug, whichever is longer.

   Non-vasectomized male patients with female partners of childbearing potential must agree to either abstain from sexual activity or agree to use a highly effective method of contraception from screening until the end of the study or for 120 days following 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 (e.g., missed or later menstrual period) at any time during study participation.

7.5 Exclusion Criteria

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

1) Use of systemic or topical corticosteroids exceeding the equivalent of 10 mg/day prednisone within 4 weeks prior to the screening visit.
2) Baseline endoscopic biopsy with ≥30 eosinophils/hpf in 5 hpf in the gastric mucosa as determined by central histology assessment of biopsies collected during the screening EGD.
3) Change in the dose of corticosteroids (systemic or topical), PPI, leukotrienes, or diet therapy within 4 weeks prior to the screening visit.
4) Treatment with any immunosuppressive or immunomodulatory drugs that may interfere with the study within 12 weeks prior to the screening visit.
5) Prior exposure to AK002 or known hypersensitivity to any constituent of the study drug.
6) Active *H. pylori* infection as confirmed by a stool antigen test for *H. pylori*.
7) History of inflammatory bowel disease, other chronic inflammatory diseases in the colon (with the exception of eosinophilic colitis), celiac disease, achalasia, or esophageal surgery.
8) History of bleeding disorders and/or esophageal varices considered to be significant by the Investigator.
9) Other significant causes of gastric and/or duodenal eosinophilia or eosinophilic granulomatosis with polyangiitis (EGPA).
10) Confirmed diagnosis of hypereosinophilic syndrome (HES).

11) Women who are pregnant, breastfeeding, or planning to become pregnant while participating in the study.

12) Presence of an abnormal laboratory value considered to be clinically significant by the Investigator.

13) Any disease, condition (medical or surgical), or cardiac abnormality, which, in the opinion of the Investigator, would place the patient at increased risk.

14) History of malignancy, except carcinoma in situ, early-stage prostate cancer, or non-melanoma skin cancers. However, patients with cancers that have been in remission for more than 5 years and are considered cured can be enrolled.

15) Treatment for a clinically significant helminthic parasitic infection within 6 months of screening.

16) Positive helminthic infection on ova and parasite (O&P) test.

17) Seropositive for Strongyloides stercoralis at screening.

18) Seropositive for HIV or hepatitis at screening, except for vaccinated patients or patients with past but resolved hepatitis, at screening. See Appendix 12.

19) Vaccination with live attenuated vaccines within 30 days prior to initiation of treatment in the study, during the treatment period, or vaccination expected within 5 half-lives (4 months) of study drug administration. This exclusion criterion does not apply to all types and formulations of vaccines authorized by FDA or other regulatory authority for the prevention of COVID-19, which may be administered before, during, or after the study. The vaccine should not be administered within 7 days before 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.

20) Participation in a concurrent interventional study with the last intervention occurring within 30 days prior to study drug administration (or 90 days or 5 half-lives, whichever is longer, for biologic products).

21) Known history of alcohol, drug, or other substance abuse or dependence that is considered by the Investigator to be ongoing and clinically significant.

22) Any other reason that in the opinion of the Investigator or the Medical Monitor makes the patient unsuitable for enrollment.

7.6 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 TEAE will be collected from the start of study drug administration in the double-blind period of the study through the start of study drug administration in the OLE period of the study, Day 225, if patient is not enrolling in the OLE period of the study, or 84 days after last dose, if ET.

Severity will be assessed using the National Cancer Institute (NCI) 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 for clinical significance and relationship to study drug. Adverse events of special interest will be noted.

Additional safety evaluations include clinical laboratory tests comprising ADA to AK002, CBC, chemistries and urinalyses, physical exams, and vital sign measurements.

The Medical Monitor will review blinded safety data throughout the study. Certain safety data (post-treatment cell differentials, as well as tissue eosinophil and [redacted]) will not be provided to study sites or to the Sponsor as it may cause bias. The designated Safety Monitor will review blinded safety data as well as post-treatment cell counts and will escalate to the Medical Monitor as needed in a manner that does not cause bias.

An independent Data Monitoring Committee (iDMC) has been convened and will meet at regularly scheduled intervals in accordance with the iDMC charter.

8. Prior and 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) for 30 days prior to the screening visit. Prior medications used for the treatment of EoD symptoms, even if they are >30 days before the screening visit, will be documented in the eCRF.

For patients participating in the OLE period, concomitant medications should be recorded in the AK002-021 double-blind treatment period database beginning after the first administration of study drug in the double-blind period of the study up until the first open-label dose is administered after the Day 176 visit. This includes the prednisone premedication administered after the Day 176 visit in the OLE period, which should be recorded in the Concomitant Medications CRF of both the AK002-021 double-blind treatment period database and the AK002-021 OLE period database.

Any medications should have been stopped as required in the exclusion criteria. Patients should be advised against taking any new medication, both prescribed and over the counter, without consulting the Investigator, unless the new medication is required for emergency use or it is a vaccine to prevent COVID-19. Immediately prior to the first infusion, study site personnel should ensure that the patient continues to meet the inclusion criteria and none of the exclusion criteria (including no receipt or use of prohibited medications).

All medications taken for the 30 days before screening and during participation in this study must be documented on the eCRF. All medications used to treat IRR or AE must be documented. All medications given as preparation for and during the conduct of the EGD and colonoscopy must also be documented.

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 in the double-blind period of the study and ending at the time of study completion or early termination of the double-blind period or the OLE period, whichever is later.

8.1 Prohibited Medications

Any biologics or other medications, such as systemic immunosuppressive or immunomodulatory drugs that may interfere with the study efficacy or safety assessments including but not limited to IL-5 modulators (e.g., benralizumab, reslizumab, mepolizumab), IL-4 and/or IL-13 antagonists (e.g., dupilumab), calcineurin inhibitors (e.g., cyclosporin, tacrolimus), mTOR inhibitors (e.g., sirolimus, everolimus), anti-metabolites (e.g., azathioprine, methotrexate, 6-mercaptopurine, leflunomide, mycophenolate mofetil), alkylating agents (e.g., cyclophosphamide), TNF inhibitors (e.g., infliximab, adalimumab), anti-IgE antibodies (e.g., omalizumab), JAK inhibitors, and eosinophil-depleting drugs (e.g., pramipexole).

Patients will be reminded to not take prohibited medications and to notify the site immediately if a prohibited medication is prescribed by another health care provider. If a prohibited medication is started during the course of the study, the patient may be withdrawn from study treatment and followed for the 12-week follow-up period. The follow-up EGD may not be performed.

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

Prohibited medication(s) given within 24 hours of an infusion, if medically necessary for the treatment of an IRR, is acceptable and not considered a deviation from the protocol.

8.2 Restricted Medications

The use of systemic corticosteroids given as pre-infusion prophylaxis or for the treatment of IRR is allowed and will not be considered a deviation from the protocol. The use of systemic or swallowed corticosteroids at a dose equivalent to >10 mg/day of prednisone for the treatment of EoD at any point in the study will be considered rescue therapy. However, the subject may remain in the study. The use of systemic or swallowed corticosteroids at a dose equivalent to >10 mg/day of prednisone is restricted and must be limited to cases of medical necessity when no other alternatives are available. The corticosteroids must be documented along with the reasons for use, and attempts should be made to discontinue the corticosteroids as early as possible.

The use of PPI during the study is allowed provided that the subject is on a stable dose during the screening period and agrees to continue on the same dose through the end of the study. Initiation of PPI therapy or an increase in the dose of an oral PPI following the screening period will be considered a rescue therapy and will only be allowed if the Investigator deems such treatment to be medically necessary. In this case, discontinuation of the PPI therapy prior to Study Week 21 should be considered if medically safe in the opinion of the Investigator.

The use of sodium cromolyn for subjects who were on a stable dose during the screening period is allowed provided that they are willing to remain on the same dose of sodium cromolyn through the end of the study. Initiation or increase in the dose of sodium cromolyn following the screening period will be considered a rescue therapy and will only be allowed if the Investigator deems such treatment to be medically necessary. In this case, discontinuation of the sodium cromolyn therapy prior to Study Week 21 should be considered if medically safe in the opinion of the Investigator.

8.3 Allowed Medications

Medications, other than those that are prohibited or restricted (Section 8.1 and Section 8.2), such as antihistamines, leukotriene antagonists, and sodium cromolyn are allowed during the study and, unless required due to unforeseen medical necessity, doses and/or dietary modifications are to remain stable.

All types and formulations of vaccines approved by FDA or other regulatory authority for the prevention of COVID-19 may be administered before, during, or after the study. The vaccine should not be administered within 7 days before and within 7 days after the administration of study drug so that any side effects caused by either of the 2 medications can be more easily determined.

Systemic or swallowed corticosteroids with a dose of ≤10 mg/day prednisone or equivalent being used at the time of study entry are acceptable as long as the dose remains stable throughout screening and during the study.

Short courses or a single use of corticosteroid therapy at doses of ≤10 mg/day of prednisone or equivalent due to unforeseen medical necessity for conditions other than the disease under study will be allowed at the discretion of the Investigator provided that the corticosteroids are discontinued prior to Study Week 21. Consideration should be given to alternative therapies whenever possible.

Swallowed or systemic corticosteroids at a dose of >10 mg are not considered prohibited under the following circumstances:

- Systemic corticosteroids given within 24 hours of the start of an infusion when medically necessary for the treatment of an IRR.
- A single dose of IV corticosteroid given during the EGD to minimize AE associated with anesthesia (e.g., nausea and vomiting after anesthesia).
- Premedication with prednisone prior to Dose 1 in the double-blind period and Dose 1 in the OLE period, as required by the protocol.
- Premedication with a systemic corticosteroid (for any dose other than Dose 1 in the double-blind period and Dose 1 in the OLE period), which has been preapproved by the Medical Monitor prior to dosing.

All medication used during the screening period and throughout the study will be documented in the CRF. Any allowed medications that are taken must remain stable throughout the study.

Medications administered for the EGD and colonoscopy are allowed. Medications administered for bowel preparation prior to colonoscopies are also allowed.

All patients will be pretreated with 80 mg prednisone the day before the first infusion.

9. Study Treatment

9.1 Formulation of Test Product and Placebo

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°C to 8°C. The AK002 formulation is CCI [redacted] pH 6.0, in sterile Water for Injection (WFI).

Placebo is supplied as a sterile liquid in a single-use 10R glass vial with a fill volume of not less than 10 mL. Placebo contains [redacted] pH 6.0, in sterile WFI.

***Note*:** AK002 and placebo will be referred to as "study drug."

9.2 Study Drug Packaging and Labeling

Study drug is supplied as a sterile liquid in a single-use 10R glass vial with a fill volume of approximately 10.6 mL. Glass vials are plugged with Teflon-coated rubber stoppers and sealed with aluminum seals.

Each vial will be labeled with the required investigational use statement, lot number, kit number, Sponsor name, and directions for storage. Each vial will also contain a tear-off label with kit number and space to document Patient ID and preparation date. This tear-off label should be applied to the IP Dose Calculation and Preparation Worksheet and maintained with the source documents.

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, the contract has been executed, and the first screened patient is entered into the IRT. 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 Dosage Regimen

Patients will be randomly assigned through the IRT system to an active dose group of 6 doses of 3 mg/kg AK002 or placebo. The exact dose will be calculated prior to each infusion and based on current patient weight. Study drug will be administered as a single peripheral intravenous infusion using an infusion pump as indicated in the study Pharmacy Manual on Days 1, 29, 57, 85, 113, and 141 (±3).

9.5 Preparation of Study Drug

A study pharmacist or designee will prepare the study drug for each infusion. Based on patient weight obtained the day of dosing, the designated study pharmacist will prepare the appropriate dilution of AK002 or placebo 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. Based on current USP 2019 guidelines,

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

The infusion must be completed within 8 hours of preparation. Preparation is when AK002/placebo 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 IV set. The IV line will 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 Study Day 1, over at least 1 hour on Study Days 29, 57, 85, 113, and 141 (±3). 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 rounding of the total infusion volume by some programmable infusion pumps, an infusion of 99 to 101 mL will be considered a complete infusion and will not be recorded as a deviation from the study.

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, steroid premedication may be used at the discretion of the Investigator and with written approval from the Medical Monitor.

The intravenous 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 (SAE) during the course of the infusion.

The initial infusion should be given over at least a 4-hour period, and the subsequent infusions should be given over at least a 1-hour period, depending on the patient's tolerance of the previous infusions and at the Investigator's discretion. Any reduction in the infusion rate schedule due to tolerability will not be considered a deviation from the protocol. All infusions must be completed within 8 hours of the study drug being mixed with NaCl. The patient will be observed for at least 1 hour after the end of each infusion as per the Investigator's discretion.

As treatment assignment during the double-blind, placebo-controlled part of the study will be masked, all eligible patients that choose to participate in the OLE period of the study will self-administer 80 mg of oral prednisone premedication 12–24 hours prior to the first OLE infusion as well.

9.7 Study Drug Storage

Study drug will be stored by the study sites at 2°C to 8ºC under lock at the designated pharmacy location. Access will be restricted to designated pharmacy staff. The 0.9% NaCl will be stored at ambient temperature, per manufacturer's requirements. All study drug and NaCl 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 quarantined and reported to the Sponsor or designee. The Sponsor will notify the site if the study drug is to be released from quarantined.

9.8 Study Drug Accountability

The site's study pharmacist/designee is responsible for maintaining accurate and current records accounting for the receipt, dispensing, preparation, use, return (or destruction), and final disposition of all investigational product (IP). All dosage calculations will be documented on the source documents. The Master IP Accountability Log 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.

Study drug will be labeled with kit numbers but will not reveal whether the kit contains active drug or placebo.

10. Patient Numbering, Stratification, Randomization, and Blinding

10.1 Patient Numbering

Each patient who provides informed consent will be assigned a patient identification number (PID) that uniquely identifies them as a patient in the study. The PID will consist of a 9-digit number:

- The first 3 digits designate the study number. For this study, the number is 221.
- The second 3 digits designate the site number.
- The last 3 digits designate the order of consent at the site (the first patient who provides consent is 001, the second patient is 002, etc.).

The patient will maintain the same PID throughout the study. If a patient signs the ICF but does not meet the inclusion/exclusion criteria or qualifies for the study but does not enroll, they may be assigned a new PID and rescreened once. Patients rescreened within 30 days of signing the initial consent will not need to sign a new ICF providing no changes have been made to the ICF.

10.2 Stratification and Randomization

To be randomized into the study, a patient must have a weekly average score of ≥3 (on a scale from 0–10) recorded for either abdominal pain, nausea, and/or diarrhea on the PRO questionnaire for at least 2 weeks during screening and an average weekly TSS ≥10 for at least 2 weeks during screening. Completion of at least 4 daily PRO questionnaires per week, for a minimum of 3 weeks during screening, is required to qualify. Patients will be randomized through the Interactive Response Technology (IRT) system.

If the patient qualifies for the study after completing all of the screening procedures on the day prior to or on the day of the first infusion (Study Day 1), the site will access the IRT system in order to stratify and randomize the patient in the study and enter the current body weight for study drug dose calculation. The site will enter the highest weekly TSS of disease activity recorded during the screening period in order to stratify patients into screening TSS <28 or ≥28 strata. The IRT system will then randomly assign the patient at a 1:1 allocation ratio to AK002 3 mg/kg for 6 doses, or placebo in a double-blind manner and will send an email to the pharmacist and/or designee detailing the kit number(s) to use to prepare the infusion.

Approximately 40 patients will be randomized to treatment with AK002 at a dose of 3 mg/kg for 6 doses, and approximately 40 patients will be randomized to placebo. A minimum number of approximately 80 patients with EoD without EG will be enrolled.

A patient is considered enrolled in the study when the patient is randomized.

For subsequent infusions on Days 29, 57, 85, 113, and 141, the coordinator will access the IRT on the day of infusion and enter the PID as well as the patient's body weight, and the system will assign the patient the dose according to their randomization number. The pharmacist and/or designee will then receive an email detailing the kit number(s) to prepare, as well as the volume of study drug to be mixed with NaCl.

Prior to each infusion, the Investigator or designee will confirm the PID recorded on the IV bag provided by the Pharmacist matches the patient. The patient identification should be confirmed and documented by a second party prior to administering the infusion, whenever possible. There will not be any unblinding information on the IRT notification to the Pharmacist or on the infusion bag provided to the site.

The assignment of treatment to AK002 or placebo will be securely retained in the IRT system until such time as designated by the Statistical Analysis Plan.

10.3 Blinding

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

- Access to the randomization codes will be strictly controlled by the IRT.
- Throughout the study, the blind should remain unbroken except for an emergency when knowledge of the patient's study medication is necessary for further management or if required for regulatory reporting. The Allakos Medical Monitor approves any emergency blind break, if at all possible, prior to the unblinding.
- The AK002 and placebo for infusion will be identical in appearance.
- Results from the analysis of blood samples for peripheral hematology differential cells will not be provided to the Investigator and Sponsor until after database lock. Real-time safety monitoring of differential cells will be conducted by the Safety Monitor.
- Results from the analysis of blood samples for PK and ADA will not be provided to the Investigator and Sponsor until after database lock.
- Results from the analysis of blood samples for histamine/tryptase tests will not be provided to the Investigator and Sponsor until after database lock, unless required for immediate safety reasons.
- After the initial infusion of study drug and prior to entering into the OLE period of the study (if applicable), results of the assessments noted below will not be provided to the Investigator and Sponsor until after database lock, so as to not introduce bias. The results will be reviewed on an ongoing basis by the Safety Monitor and escalated as appropriate.
  - Differential cell counts including neutrophils, eosinophils, basophils, monocytes, and lymphocytes.
  - Enumeration of eosinophils and CCI from the Day 169 EGD and colonoscopy biopsies.

Other than under the conditions described above, the study blind will be revealed on completion of the study as noted in Section 16.4.

10.4 Breaking the Blind

Breaking the blind in a clinical trial on an emergency basis by the site should only occur when knowledge of the treatment to which a patient was allocated would have implications for the emergency medical management of the patient, if required for regulatory reporting, or if there is a pregnancy during the pregnancy reporting period.

If necessary, emergency breaking of the blind can be conducted through the IRT by registered site users and/or the Medical Monitor. Whenever possible, the Investigator should contact the Medical Monitor before an emergency breaking of the blind. Reason for unblinding, person conducting the unblinding, personnel who know the unblinded treatment, and date/time of unblinding will be recorded.

11. Study Procedures and Guidelines

Table 2 provides the schedule of events depicting the required testing procedures to be performed for the duration of the study.

Provided visit windows must be followed and deviations reported to the Institutional Review Board (IRB) per IRB reporting requirements. All dosing visits must be separated by at least 22 days and no more than 34 days unless directed otherwise by Allakos (the interval count starts the day after the visit and includes the day of the next visit).

The Day 169 visit is critical for the primary endpoint, and it is essential that the interval between the last dose of study drug (e.g., the Day 141 visit) and the Day 169 EGD or early termination EGD be at least 22 days and no more than 34 days (the interval count starts the day after the visit and includes the day of the next visit). A visit conducted outside of this interval may impact the efficacy assessment and must be avoided. Contact Allakos immediately if this occurs or if it may occur.

When multiple evaluations are scheduled at the same time point, the priority for each will be as follows:

- CCI (self-administered format) (Appendix 2) should be completed at the beginning of the study visit before any other assessments or procedures.
- PRO questionnaire (Appendix 1), followed by additional questions regarding dysphagia and constipation (Appendix 10), should be completed by each patient daily (at approximately the same time each day) during the screening, treatment, and follow-up periods.
- Patients will rate their impression of disease severity CCI Appendix 8) and disease improvement CCI Appendix 9) at specified time points during the study.

- Vital signs will be obtained after the patient has been at rest for ≥5 minutes.
- Physical examinations can be performed, and urine samples can be collected either before or after other evaluations, unless otherwise specified.

11.1 Dietary and Lifestyle Restrictions

Patients should maintain the same diet and food restrictions from the screening visit through the End-of-Study visit. Compliance with previous dietary and lifestyle restrictions will be captured in the eCRF at each study visit.

11.2 Pharmacodynamic/Efficacy-Related Procedures

11.2.1 EG/EoD PRO Questionnaire

An electronic version of the EG/EoD 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 electronic data capture system (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 questionnaire should be completed per day, and the recall period should not be more than approximately 24 hours long. This information will be manually captured and entered into the EDC by the study site.

Post-dose PRO completion during Study Days 155–168 is critical for the primary endpoint, and the study site should carefully monitor PRO completion compliance by the patient during this period and immediately contact patients who are not sufficiently compliant. Poor PRO completion compliance during Study Days 155–168 may impact the efficacy assessment and must be avoided. Contact Allakos immediately if this occurs or if it may occur.

Additional Questions: Patients will complete an extra question each about dysphagia and constipation during the screening period and throughout the study. A paper version of these questions (Appendix 10) is available if the website is not accessible or the patient does not have internet access. These will be completed following the electronic PRO questionnaire.

11.2.2 [redacted]

An electronic version of the [redacted] (Appendix 2) will be completed by the patient at the screening visit, predose on infusion Days 1, 29, 57, 85, 113, and 141 and on follow-up Day 176 and Day 197 or 35 (±3) days and 56 (±3) days after last dose of study drug if ET. This information will be automatically captured and maintained in the EDC. 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 [redacted] and [redacted]

An electronic version of the [redacted] (Appendix 9) will be completed by the patient on Study Day 7 and Day 28 and Day 225 or ET. An electronic version of the [redacted] (Appendix 8) will be completed by the patient on Screening Day 19 as well as on Study Day 7 and Day 28 and Day 225 or ET. A paper version of these questionnaires 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.

11.2.4 EGD and Colonoscopy with Biopsy

An EGD and colonoscopy with biopsy will be performed during the screening period and on Day 169 (±3) or 28 (±3) days after last dose of study drug if ET. If the last infusion on Day 141 occurs outside the protocol-specified window, the EGD and colonoscopy date should be moved so that it occurs 28 (±3) days from the date of last dose, even if this does not fall on Day 169 (±3).

The Day 169 visit is critical for the primary endpoint, and it is essential that the interval between the last dose of study drug (e.g., the Day 141 visit) and the Day 169 EGD or early termination EGD be at least 22 days and no more than 34 days (the interval count starts the day after the visit and includes the day of the next visit). A visit conducted outside of this interval may impact the efficacy assessment and must be avoided. Contact Allakos immediately if this occurs or if it may occur.

Biopsy samples will be collected on the same day, whenever possible, according to standardized instructions and will be sent to the central laboratory (or designee) for fixing and staining. Additional biopsies will be collected for exploratory analysis. Any stored tissue from biopsies may be used for exploratory analysis. Patients with a history of EoE and/or with a score of ≥3 on the dysphagia question during screening will also have esophageal biopsies collected during the EGD at screening and postdose.

A blinded central reader will report, among other things, maximum number of eosinophils per hpf and maximum number of tryptase-positive mast cells per hpf, and gastric biopsies will be graded using the Sydney System on inflammation, metaplasia, atrophy, and reactive gastropathy. The Marsh Scale Classification will be used to grade duodenal samples.

Post-treatment EGD and colonoscopy results will not be provided to the Investigator and Sponsor until after database lock. The Safety Monitor will review the EGD and colonoscopy results and report any issues for escalation to the Medical Monitor and the clinical site, as appropriate, while maintaining the blind.

The screening EGD and colonoscopy with biopsy will be used to determine the following inclusion/exclusion criteria as related to the EGD only, and the results must be available from the central reader before the patient's eligibility can be verified.

- Inclusion Criterion #3: Baseline endoscopic biopsy with ≥30 eosinophils/hpf in at least 3 hpf in the duodenum without any other significant cause for the eosinophilia.
- Exclusion Criterion #2: Baseline endoscopic biopsy with ≥30 eosinophils/hpf in 5 hpf in the gastric mucosa.
- Exclusion Criterion #6: Active *H. pylori* infection as confirmed by stool antigen test for *H. pylori*.

  ***Note*:** A diagnosis of active *H. pylori* at screening (by stool antigen test or as detected in tissue biopsies by the central pathologist) will result in a screen failure. After *H. pylori* treatment and an additional 6 weeks later, the subject may be reconsented and will receive a new subject identification number.
- Exclusion Criterion #7: History of IBD, other chronic inflammatory diseases in the colon (with the exception of eosinophilic colitis), celiac disease, achalasia, or esophageal surgery.

For the colonoscopies with biopsy, a central reader will report, among other things, maximum number of eosinophils per hpf and maximum number of tryptase-positive mast cells per hpf for each colonic biopsy specimen. Samples from the colonoscopy will include biopsies of the terminal ileum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. Instructions on collection and processing of biopsies are detailed in the Histology Manual.

Prior EGD and colonoscopy biopsy samples may be used for eligibility as long as the procedures were performed within 45 days of the AK002-021 screening window for the AK002-021 study and were performed and centrally assessed using the same criteria as for the AK002-021 study, and there were no changes to EoD therapy following the EGD.

11.2.5 Complete Blood Count with Differential

Blood will be obtained for CBC with differential, including absolute eosinophil count, at the screening visit, once on Days 8, 15, and 169, and during each follow-up visit or ET visit, as well as predose and 1 hour (±15 minutes) postdose on Days 1, 29, 57, 85, 113, and 141. The blood sample will be processed and shipped in accordance with the Laboratory Manual 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).

The blood differential test results (neutrophils, eosinophils, basophils, monocytes, and lymphocytes) will be blinded from the Investigator and Sponsor from postdose Day 1 through Day 225 or ET and until database lock has occurred. As described in the Investigator's Brochure, these are part of the expected effects of AK002 and could potentially serve to introduce bias in blinded members of the study. The Safety Monitor will have real-time access to these laboratory results and will review and escalate any concerns/issues to the Medical Monitor and/or the site as appropriate. An unscheduled CBC with differential may be collected if requested by the Safety Monitor. All panic alerts for blinded values will be sent to the Safety Monitor and evaluated in real time.

11.2.6 Baseline Diet Assessment and Compliance

During the screening visit the Investigator or designee will ask the patient a standardized series of dietary assessment questions (Appendix 3). This baseline diet assessment involves questions regarding food behavior and patterns, as well as types of foods generally avoided, and will serve to establish the baseline diet. Answers will be documented in the source documents and recorded in the eCRF.

This baseline diet should be maintained, as much as possible, throughout the course of the study, even if symptoms improve. Compliance with the baseline diet will be assessed at study visits on Days 1, 15, 29, 57, 85, 113, 141, 176, 197, and 225 or 35,56, and 84 (±3) days after last dose of study drug if ET. Whether or not the patient has maintained the baseline diet and what deviations were made, if applicable, should be documented in the source documents and the eCRF.

11.2.7 Previous Treatments and Procedure Review

During the screening visit the Investigator or designee will ask the patient about previous EGD and colonoscopy procedures and various treatments or methods of symptom control that they have tried in relation to their EoD symptoms. These may be under the supervision of a doctor or self-attempted by the patient. These may include medications (prescription or over-the-counter),

food type/eating avoidance or adaptive behaviors, as well as alternative medicine (i.e., acupuncture or hypnotic therapy). See Appendix 11.

11.3 Safety-Related Procedures

11.3.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at screening and at study visits if changes are made. Dose, route, unit, frequency of administration, indication for administration, and dates of medication will be captured. Any prior medication received within 30 days before screening and during the study through Day 225 (±3) or 84 (±3) days after last dose of study drug, if ET, will be recorded, or through the first dose of study drug if patient enters the OLE period of the study. Any medications taken for EoD or EoD-related symptoms at any time (even if longer than 30 days before screening) should be listed as concomitant medications, even if the medications were discontinued prior to study participation.

For patients participating in the OLE period, concomitant medications should be recorded in the AK002-021 treatment period database up until the first open-label dose is administered after the Day 176 visit. This includes the prednisone premedication administered prior to the first dose administration visit in the OLE period, which should be recorded in the Concomitant Medications CRF of both the AK002-021 treatment period database and the AK002-021 OLE period database. Rescue medications and procedures must be documented as rescue treatment in the source documents and on the Prior and Concomitant Medications eCRF.

11.3.2 Complete Physical Examination

A complete physical exam will be performed by either the Investigator or a qualified designee during the screening visit. A complete physical exam will include the following body system or organ assessments: skin; head, eyes, ears, nose, and throat (HEENT); thyroid; lungs; cardiovascular; abdomen; extremities; lymph nodes; and a brief neurological examination.

11.3.3 Body Weight and Height

At screening, height in cm and weight in kg will be measured and body mass index (BMI) will be calculated. On Days 1, 29, 57, 85, 113, and 141 only, weight will be calculated predose and used to determine the amount of study drug to be administered. Body weight will be entered into the IRT for each dosing visit and will also be recorded on the IP Dose Calculation and Preparation Worksheet that the pharmacist will maintain and document each patient's dose calculations. Body weight should be collected on site on the day of each study drug infusion or the day prior to each infusion. Body weight will also be captured on Days 176 (±3), 197 (±3), and 225 (±3) or 35 (±3), 56 (±3), and 84 (±3) days after last dose of study drug if ET.

11.3.4 Stool Sample for Ova and Parasite

At screening, fecal collection kits will be provided to patients for the ova and parasite test. Patients will return the sample to the site during the screening period, within 1 day of collection. The site will ship samples to a central laboratory where they will be tested for the presence of ova and/or parasites. A negative result for helminthic parasites must be obtained from the central laboratory prior to randomization into the study (Day 1).

A sample collected and analyzed by the central laboratory within 30 days prior to screening may be used to satisfy eligibility for the AK002-021 study, and a duplicate sample does not have to be collected.

11.3.5 Symptom-Directed Physical Examination

A symptom-directed physical exam 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 during the treatment period and follow-up period. New, abnormal physical exam findings must be documented and will be followed by the Investigator or Subinvestigator at the next scheduled visit or sooner if clinically indicated or referred to a non-study physician.

11.3.6 Electrocardiogram

An ECG will be obtained during screening after the patient has been in the required position for ≥5 minutes and before any blood draw. The Investigator or Subinvestigator will review and assess any abnormalities on the ECG in terms of clinical significance. The ECG (without intensive QT analysis) will be used to identify diseases or conditions that would put the patient at increased risk if participating in a clinical study, so this should be taken into consideration when evaluating eligibility for entry into the study.

11.3.7 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 when vital signs will be obtained as described below).

On dosing days, vital signs will be measured within 30 minutes predose, 15 (±5) minutes after the start of infusion, immediately following the end of infusion (+15 minutes), and just prior to discharge. Refer to the schedule of assessments in Table 2.

11.4 Clinical Laboratory Measurements

Blood and urine samples for clinical safety laboratory tests will be collected at the time points described below and in Table 2. 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 lab may not be able to provide results in a timely fashion due to staff reductions, shipping issues, or other factors associated with the coronavirus 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 laboratory 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.
  - Requires a patient to receive treatment.

Blood will be obtained for CBC with differential as described in Section 11.2.5.

11.5 Blood Chemistry Profile

Blood will be obtained for chemistry tests at screening and predose on dosing Days 1, 29, 57, 85, 113, and 141 as well as Days 8, 15, 169, 176, 197, and 225 or 28 (±3), 35 (±3), 56 (±3), and 84 (±3) days after last dose of study drug if ET. The blood sample will be processed and shipped in accordance with the Laboratory Manual and laboratory kit instructions. A central laboratory will analyze the serum sample and provide results for chemistry tests including sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, creatine kinase, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), and lactate dehydrogenase.

11.5.1 Pregnancy Test and Follicle-Stimulating Hormone

A serum pregnancy (hCG) test will be completed for all female patients of childbearing potential. Women who are surgically sterile (tubal ligation, partial or total 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. At screening, FSH levels will be tested for female patients to confirm postmenopausal vs. childbearing status. Both FSH and hCG samples will be processed by the central laboratory.

Patients with FSH levels ≤30 MIU/mL are considered to be of childbearing potential. For patients of childbearing potential, the site will perform a urine dipstick pregnancy test prior to each study drug dosing and at Day 176 and Day 197 (±3) or 35 (±3) days and 56 (±3) days after last dose of study drug if ET. This test is to be assessed by the study staff prior to the start of each study drug infusion. 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 up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence of absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. If the patient received AK002, any SAE experienced during pregnancy must be reported on the SAE Report Form.

11.5.2 Urinalysis

Urine will be obtained for urinalysis at screening, on Day 29, at the ET visit, and symptom-based, as necessary. The urine sample will be processed and shipped in accordance with the Laboratory Manual and laboratory kit instructions. A central laboratory will analyze the urine sample for specific gravity, pH, protein, glucose, ketones, blood, and leukocyte esterase.

11.5.3 Serology

Blood will be obtained at screening for serology tests including hepatitis B surface antigen (HBsAG), hepatitis C antibody, hepatitis B core antibody (anti-HBc), and human immunodeficiency virus (HIV). The blood sample will be processed and shipped to the central laboratory in accordance with the Laboratory Manual and lab kit instructions. A positive result will be verified by appropriate reflex testing. A positive result, if clinically significant (and not due to previous vaccination or resolved disease or exposure) will exclude the patient from enrollment. See Appendix 12.

11.5.4 Anti-AK002 Antibodies

Blood will be collected for determination of ADA at screening, and predose on Days 1, 29, 57, 85, and on Day 169 and Day 225 or 84 (±3) days after last dose of study drug if ET. An unscheduled blood sample for ADA may also be obtained if a related AE suspected of being associated with immunogenicity occurs. The serum sample will be collected predose and processed and shipped in accordance with the laboratory manual and lab kit instructions.
A central laboratory will analyze the sample for anti-AK002 antibodies using a validated assay method.

11.5.5 Blood for Pharmacokinetics and Storage

Blood samples for serum PK assessments will be collected during the screening period as well as predose on dosing Days 29, 57, 85,113, and 141 and on Days 8, 15, 169, 176, 197, and 225 or 28, 35, 56, and 84 (±3) days after last dose of study drug, if ET. The serum samples will be collected predose and processed and shipped frozen in accordance with the study Laboratory Manual and lab kit instructions.

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 laboratory manual.

11.5.6 Blood for Histamine and Tryptase

If anaphylaxis is suspected, a blood sample should be obtained for plasma histamine level and tryptase within 1–2 hours of the onset of symptoms. The sample will be sent to the central laboratory for processing. Refer to Appendix 6 for more details.

11.5.7 Blood for IgE

Blood will be collected for determination of serum IgE levels and sent to the central laboratory for processing. Blood will be collected during screening and on follow-up Day 176 (±3) or 35 (±3) days after last dose of study drug if ET.

11.5.8 Blood for Strongyloides stercoralis

Blood collected for the screening serology sample will be tested for Strongyloides stercoralis. The sample will be processed by the central laboratory. A negative result must be available prior to the first dose of study drug.

In case of a positive Strongyloides stercoralis test result, the patient must be screen failed and should be treated with standard therapies. If symptoms remain consistent, patient may be reconsented and receive a new patient number 4 weeks after completion of therapy.

11.5.9 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 or study sites, and if this is required, will be consented through the site and not listed in the AK002-021 ICF.

11.6 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 SC 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.

12. Evaluations and Procedures by Visit

Evaluations and procedures by visit are shown in Table 2.

General Information:

- All recorded clock times should utilize a 24-hour clock.
- Day 1 is the day of the first infusion.
- Procedures for screening may be performed over the course of multiple visits prior to the first infusion.

12.1 Screening Period

1) Obtain written informed consent.
2) Assign the participant a PID.
3) Begin the collection of SAE related to any screening activities.
4) Collect demographics and medical history.
5) Record prior and concomitant medications.
6) Determine body weight and height.
7) Activate patient access to the ePRO questionnaire portal and instruct patient on use of the website to complete the questionnaire(s). Use the ePRO Teaching Tool to instruct the patient on use of the electronic platform (Appendix 7).
8) CCI [redacted] to be completed by the patient.
9) Perform baseline diet assessment.
10) Complete previous treatments and procedure review.
11) Obtain vital signs before blood draws and after patient at rest ≥5 minutes.

12) Perform a complete physical examination.

13) Obtain a 10-lead or 12-lead ECG before blood draw.

14) Collect the following samples for the central laboratory:

    a) Blood for CBC with differential

    b) Blood for Chemistry (sample to be tested for FSH and hCG if patient is of childbearing potential)

    c) Urinalysis

    d) Blood for serology testing (includes Strongyloides stercoralis)

    e) Blood for PK

    f) Blood for ADA

    g) Blood for total serum IgE

15) Provide patient a stool collection kit and ask patient to provide a stool sample while on site or return it to the site within 1 day of collection.

16) Perform a screening EGD and colonoscopy with biopsy following instructions provided by Allakos any time during the screening period. The EGD and colonoscopy should take place on the same day in order to minimize effects of procedure premedication on the PRO scores. Patient should arrive fasting for the EGD procedure as specified by instructions from the EGD provider.

17) CCI to be completed by the patient on screening Day 19 (not a clinic visit).

18) Using results from the central histology reader, confirm that the eosinophil count from the gastric and/or duodenal biopsies qualify the patient for the study and no exclusionary criteria are found on the EGD or colonoscopy.

19) Review all ePRO scores. Since the bowel preparations could artificially increase the scores, exclude ePRO scores from the day before and the day of colonoscopy when assessing eligibility criteria.

12.2 Prior to Day 1

The following procedures will be performed prior to Day 1:

1) Patient should self-administer 80 mg oral prednisone (or alternative premedication approved by the Medical Monitor) 12–24 hours prior to infusion start. Patient should remember what time they took the premedication. This 80 mg oral prednisone is only allowed on Day 1, unless preapproved by the Allakos Medical Monitor.

12.3 Day 1 – Randomization/Infusion 1

1) Prior to the infusion:

   a) Assess the patient for SAE related to screening procedures.

   b) Confirm continuing eligibility.

   c) Document any changes to health status.

   d) Document any changes to concomitant medications.

   e) Document any changes to baseline diet.

   f) CCI [redacted]

   g) Confirm CCI was completed electronically on Screening Day 19. If it was not completed, have patient complete a paper version of the questionnaire.

   h) Determine body weight.

   i) Perform urine pregnancy test if patient is of childbearing potential.

   j) Collect vital signs within 30 minutes of the start of the infusion.

   k) Perform symptom-directed physical exam, if needed.

   l) Blood for CBC with differential

   m) Blood for Chemistry

2) Prior to randomizing the patient in the IRT system, the site will identify the highest weekly TSS of disease activity recorded during the screening period (prior to Day 1) in order to stratify patients to TSS ≥28 or TSS <28 as captured in the patient PRO. The study coordinator or designee will enter the highest weekly TSS into the IRT on Study Day 1 to stratify the patient.

3) The IRT system will randomly assign the patient to AK002 at a dose 3 mg/kg for 6 doses or placebo in a double-blind manner and will send an email to the pharmacist and/or designee detailing the kit number(s) to use to prepare the infusion, the dose to prepare (3 mg/kg), and the patient's body weight.

4) The study pharmacist will prepare study drug using the weight obtained at the visit. Refer to the Pharmacy Manual for details on dose preparation.

5) Infusion of Study Drug:

   a) Infuse 100 mL of study drug over at least 4 hours using an infusion pump. See the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.

b) Collect vital signs 15 (±5) minutes after the start of infusion.

c) If anaphylaxis is suspected, a sample of blood should be obtained for plasma histamine level and tryptase within 1–2 hours of the onset of symptoms. Also, an unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

6) Post-infusion:

a) Collect vital signs within 15 minutes of the end of the infusion.

b) Collect blood for CBC with differential 1 hour (±15 minutes) after the end of the infusion.

c) Observe the patient for at least 1 hour after the end of infusion. Collect vital signs just prior to discharge.

12.4 Day 7 (not a Clinic Visit)

1) CCI (Appendix 8)

2) CCI (Appendix 9)

12.5 Day 8 (±2)

1) Assess the patient for AE and SAE.

2) Document any changes to concomitant medications.

3) Blood for CBC with differential

4) Blood for Chemistry

5) Blood for PK

12.6 Day 15 (±2)

1) Assess the patient for AE and SAE.

2) Document any changes to concomitant medications.

3) Assess baseline diet compliance.

4) Assess daily diary compliance (including additional questions).

5) Collect vital signs

6) Perform symptom-directed physical exam, as needed

7) Blood for CBC with differential

8) Blood for Chemistry

9) Blood for PK

12.7 Day 28 (not a Clinic Visit)

1) CCI (Appendix 8)
2) CCI (Appendix 9)

12.8 Day 29 (±3) –Infusion 2

1) Prior to the infusion:
   a) Assess the patient for AE and SAE.
   b) Document any changes to concomitant medications.
   c) Assess baseline diet compliance.
   d) Assess daily diary compliance (including additional questions).
   e) CCI
   f) Determine body weight
   g) Urinalysis
   h) Perform urine pregnancy test if patient is of childbearing potential.
   i) Collect vital signs within 30 minutes of the start of the infusion.
   j) Perform symptom-directed physical exam, as needed.
   k) Blood for CBC with differential
   l) Blood for Chemistry
   m) Blood for PK
   n) Blood for ADA
   o) The IRT will be accessed, and the patient's PID and body weight will be entered.
2) The study pharmacist will prepare study drug using the current body weight obtained and the dosage (3 mg/kg) and kit number(s) provided by the IRT.
3) Infusion of Study Drug:
   a) Infuse 100 mL of study drug over at least 1 hour using an infusion pump. See the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.
   b) Collect vital signs 15 (±5) minutes after the start of infusion.
   c) If anaphylaxis is suspected, a sample of blood should be obtained for plasma histamine level and tryptase within 1–2 hours of the onset of symptoms. Also, an unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

4) Post-infusion:

   a) Collect vital signs within 15 minutes of the end of the infusion.

   b) Collect blood for CBC with differential 1 hour (±15 minutes) after the end of the infusion.

   c) Observe the patient for at least 1 hour after the end of the infusion. Collect vital signs just prior to discharge.

12.9 Day 57 (±3) – Infusion 3

1) Prior to the infusion:

   a) Assess the patient for AE and SAE.

   b) Document any changes to concomitant medications.

   c) Assess baseline diet compliance.

   d) Assess daily diary compliance (including additional questions).

   e) CCI [redacted]

   f) Determine body weight.

   g) Perform urine pregnancy test if patient is of childbearing potential.

   h) Collect vital signs within 30 minutes of the start of the infusion.

   i) Perform symptom-directed physical exam, as needed.

   j) Blood for CBC with differential

   k) Blood for Chemistry

   m) Blood for PK

   n) Blood for ADA

2) The IRT will be accessed, and the patient's PID and weight will be entered.

3) The study pharmacist or designee will prepare study drug using the weight obtained at the visit and the dosage (3 mg/kg) and kit number(s) provided by the IRT.

4) Infusion of Study Drug:

   a) Infuse 100 mL of study drug over at least 1 hour using an infusion pump. See the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.

   b) Collect vital signs 15 (±5) minutes after the start of infusion.

c) If anaphylaxis is suspected, a sample of blood should be obtained for plasma histamine level and tryptase within 1–2 hours of the onset of symptoms. Also, an unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

5) Post-infusion:

a) Collect vital signs within 15 minutes of the end of the infusion.

b) Collect blood for CBC with differential 1 hour (±15 minutes) after the end of the infusion.

c) Observe the patient for at least 1 hour after the end of the infusion. Collect vital signs just prior to discharge.

12.10 Day 85 (±3) – Infusion 4

1) Prior to the infusion:

a) Assess the patient for AE and SAE.

b) Document any changes to concomitant medications.

c) Assess baseline diet compliance.

d) Assess daily diary compliance (including additional questions).

e) CCI [redacted]

f) Determine body weight.

h) Perform urine pregnancy test if patient is of childbearing potential.

i) Collect vital signs within 30 minutes of the start of the infusion.

j) Perform symptom-directed physical exam, as needed.

k) Blood for CBC with differential

l) Blood Chemistry

m) Blood for PK

n) Blood for ADA

2) The IRT will be accessed, and the patient's PID and body weight will be entered.

3) The study pharmacist will prepare study drug using the weight obtained at the visit and the dosage (3 mg/kg) and kit number(s) provided by the IRT.

4) Infusion of Study Drug:

   a) Infuse 100 mL of study drug over at least 1 hour using an infusion pump. See the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.

   b) Collect vital signs 15 (±5) minutes after the start of infusion.

   c) If anaphylaxis is suspected, a sample of blood should be obtained for plasma histamine level and tryptase within 1–2 hours of the onset of symptoms. Also, an unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

5) Post-infusion:

   a) Collect vital signs within 15 minutes of the end of the infusion.

   b) Collect blood for CBC with differential 1 hour (±15 minutes) after the end of the infusion.

   c) Observe the patient for at least 1 hour after the end of the infusion. Collect vital signs just prior to discharge.

12.11 Day 113 (±3) – Infusion 5

1) Prior to the infusion:

   a) Assess the patient for AE and SAE.

   b) Document any changes to concomitant medications.

   c) Assess baseline diet compliance.

   d) Assess daily diary compliance (including additional questions).

   e) CCI [redacted]

   f) Determine body weight.

   h) Perform urine pregnancy test if patient is of childbearing potential.

   i) Collect vital signs within 30 minutes of the start of the infusion.

   j) Perform symptom-directed physical exam, as needed.

   k) Blood for CBC with differential

   l) Blood for Chemistry

   m) Blood for PK

2) The IRT will be accessed, and the patient's PID and body weight will be entered.

3) The study pharmacist will prepare study drug using the current weight and the dosage (3 mg/kg) and kit number(s) provided by the IRT.

4) Infusion of Study Drug:

   a) Infuse 100 mL of study drug over at least 1 hour using an infusion pump. See the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.

   b) Collect vital signs 15 (±5) minutes after the start of the infusion.

   c) If anaphylaxis is suspected, a sample of blood should be obtained for plasma histamine level and tryptase within 1–2 hours of the onset of symptoms. Also, an unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

5) Post-infusion:

   a) Collect vital signs within 15 minutes of the end of the infusion.

   b) Collect blood for CBC with differential 1 hour (±15 minutes) after the end of the infusion.

   c) Observe the patient for at least 1 hour after the end of the infusion. Collect vital signs just prior to discharge.

12.12 Day 141 (±3) – Infusion 6

1) Prior to the infusion:

   a) Assess the patient for AE and SAE.

   b) Document any changes to concomitant medications.

   c) Assess baseline diet compliance.

   d) Assess daily diary compliance (including additional questions).

   e) CCI [redacted]

   f) Determine body weight.

   h) Perform urine pregnancy test if patient is of childbearing potential.

   i) Collect vital signs within 30 minutes of start of the infusion.

   j) Perform symptom-directed physical exam, as needed.

   k) Blood for CBC with differential

   l) Blood for Chemistry

   m) Blood for PK

2) The IRT will be accessed, and the patient's PID and body weight will be entered.

3) The study pharmacist will prepare study drug using the current weight and the dosage (3 mg/kg) and kit number(s) provided by the IRT.

4) Infusion of Study Drug:

   a) Infuse 100 mL of study drug over at least 1 hour using an infusion pump. See the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.

   b) Collect vital signs 15 (±5) minutes after the start of the infusion.

   c) If anaphylaxis is suspected, a sample of blood should be obtained for plasma histamine level and tryptase within 1–2 hours of the onset of symptoms. Also, an unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

5) Post-infusion:

   a) Collect vital signs within 15 minutes of the end of the infusion.

   b) Collect blood for CBC with differential 1 hour (±15 minutes) after the end of the infusion.

   c) Observe the patient for at least 1 hour after the end of the infusion. Collect vital signs just prior to discharge.

   d) Schedule EGD and colonoscopy for Day 169 (±3).

12.13 Day 169 (±3) or 28 (±3) Days after Last Dose of Study Drug if ET – Follow-up EGD and Colonoscopy

1) Patient should arrive fasting for the EGD procedure as specified by instructions from the EGD provider.

2) Blood for CBC with differential

3) Blood for Chemistry

4) Blood for PK

5) Blood for ADA

6) Collect AE, SAE, and changes in baseline diet. Collect all concomitant medications provided to the patient during the EGD.

7) Perform EGD and colonoscopy with biopsy following procedures provided by Allakos and all EGD facility standard operating procedures (SOP). EGD and colonoscopy should take place on the same day.

For Early Termination: Perform EGD and colonoscopy 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 and colonoscopy as soon as possible.

If Day 141 (Infusion 6) occurs outside the protocol window, do ***not*** conduct the EGD and colonoscopy on Day 169 but rather on a day that is 28 (±3) days after last dose of study drug. Contact Allakos for more information.

12.14 Day 176 (±3) or 35 (±3) Days after Last Dose of Study Drug if ET – Follow-up Visit 1

1) Assess the patient for AE and SAE.
2) Document any changes to concomitant medications.
3) Assess baseline diet compliance.
4) Assess daily diary compliance (including additional questions).
5) CCI [redacted]
6) Determine body weight.
7) Collect vital signs.
8) Perform symptom-directed physical exam, as needed.
9) Blood for CBC with differential
10) Blood for Chemistry
11) Blood for PK
12) Blood for total serum IgE
13) Urine pregnancy test if patient is of childbearing potential
14) Patients who enter the OLE period of the study will begin extension dosing 1 day after completing the Day 176 procedures for the double-blind period of Protocol AK002-021. Patients may receive the required premedication for the first OLE dosing after all of the double-blind Day 176 procedures have been completed.

    Patients will not complete the Day 197 or Day 225 procedures under the double-blind period of the study. Open-label dosing and follow-up will occur under the OLE schedule for Study AK002-021 (Table 8).

Eligible patients who choose to participate in the OLE period will begin following the OLE Schedule of Assessments (Table 8 in Appendix 13) and will receive the first dose of open-label AK002 after Day 176 and after self-administering 80 mg prednisone premedication 12–24 hours prior to the first dose of AK002 in the OLE period of the protocol.

For Early Termination: Perform this visit 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. If only 1 ET visit is possible, EGD with colonoscopy and Follow-up Visit 1 may occur on the same day. Blood draws should occur prior to EGD and colonoscopy medications, if possible.

12.15 Day 197 (±3) or 56 (±3) Days after Last Dose of Study Drug if ET – Follow-up Visit 2

1) Assess the patient for AE and SAE.
2) Document any changes to concomitant medications.
3) Assess baseline diet compliance.
4) CCI [redacted]
5) Determine body weight.
6) Collect vital signs.
7) Perform symptom-directed physical exam, as needed.
8) Urine pregnancy test if patient is of childbearing potential
9) Blood for CBC with differential
10) Blood for Chemistry
11) Blood for PK

For Early Termination: Perform this visit 56 (±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 56 days after last dose of study drug, perform the visit as soon as possible.

12.16 Day 225 (±3) or 84 (±3) Days after Last Dose of Study Drug if ET

1) Assess the patient for AE and SAE.
2) Document any changes to concomitant medications.
3) Assess baseline diet compliance.
4) Perform symptom-directed physical exam, as needed.

5) Determine body weight.

6) Collect vital signs.

7) Blood for CBC with differential

8) Blood for Chemistry

9) Blood for ADA

10) Blood for PK

11) Urinalysis

12) CCI (Appendix 8)

13) CCI (Appendix 9)

For Early Termination: Perform this visit 84 (±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 84 days after last dose of study drug, perform the visit as soon as possible.

13. Adverse Event Reporting and Documentation

13.1 Adverse Events

In accordance with 21 Code of Federal Regulation (CFR) 312.32(b) and International Conference on Harmonisation (ICH) Guidance E2A, an AE is any untoward medical occurrence in a clinical investigation of a subject 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 exams, 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 significant worsening from baseline does not occur.
- Signs or symptoms of the disorder being studied unless they become more severe or occur with greater frequency than occurring at baseline.
- Normal progression of the disorder being studied unless it is more severe per Investigator judgment 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 in the double-blind period of the study and ending at the time of study completion or ET of the double-blind period or the OLE period, whichever is later.

For patients participating in the OLE period, AE will be recorded in the CRF of the AK002-021 double-blind treatment period database up until the start of the first open-label infusion after the Day 176 visit and recorded in the CRF of the AK002-021 OLE period database beginning from the start of the first open-label infusion after the Day 176 visit.

13.2 Serious Adverse Events

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

- Death
- A life-threatening AE that places the subject 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 subject.
- 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 beginning after the first administration of study drug in the double-blind period of the study and ending at the time of study completion or ET of the double-blind period or the OLE period, whichever is later.

If the SAE is related to a screening procedure, it will be captured from the date of informed consent.

13.3 Adverse Events of Special Interest

Adverse events of special interest (AESI) for this study include:

- Malignancies confirmed by histopathological report. Mast cells and eosinophils are part of the normal immune response. By decreasing their function, AK002 could theoretically increase the risk of malignancy.
- Parasitic infections confirmed by positive clinical laboratory test. (Eosinophils are believed to be involved in protecting the body from parasitic infections. 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 time of the first infusion of study drug in the double-blind period of the study and ending at the time of study completion or ET of the double-blind period or the OLE period, whichever is later. Any new AESI or new information related to a previously reported AESI must be recorded in the AE eCRF and designated as an "AE of special interest."

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 "IRR." Common symptoms of IRR include but are not limited to:

- 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.

13.5 Anaphylaxis

A suspicion of anaphylaxis will be carefully monitored and treated according to standard of care. Emergency crash cart equipment and medications, including multiple doses of epinephrine, vasopressors, and bronchodilators, will be available at all times during the conduct of the study.

To define anaphylactic reactions in a consistent and objective manner, all AE of suspected anaphylaxis will be evaluated using Sampson's Criteria for Anaphylaxis (Appendix 6).
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, they should 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 AE eCRF as separate AE. The Investigator (or qualified Subinvestigator) must assign the following AE attributes listed below and is responsible for ensuring this information is recorded in the source documentation.

13.6.2 Assessment of Intensity

Investigators will use their clinical judgment as well as the guidelines laid out in the NCI CTCAE (version 5.0 or most current version) tables to assess the intensity of each AE and SAE (Table 3 and Appendix 4).

Table 3 Adverse Event Severity per CTCAE

Grade	CTCAE 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 (ADL).
3	Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	Life-threatening consequences, urgent intervention indicated.
5	Death related to AE.

* CTCAE v. 5.0: Grade refers to the severity of the AE. The CTCAE displays Grades 1–5 with unique clinical descriptions of severity for each AE based on this general guideline.

The term “severe” is a measure of intensity, and a severe AE is not necessarily a SAE.

When the intensity of an AE changes more than once a day, the maximum severity for the event should be entered into the AE 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 their clinical judgment as well as the guidelines in Table 4 to assess the relationship between study drug and AE.

Table 4 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 re-challenge test, if possible). Another etiology is considerably less likely.
Possible	The event cannot be explained by the subject'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 subject'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 their clinical judgment as well as the guidelines in Table 5 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.

Table 5 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 subject'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 subject'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, study drug temporarily withdrawn, 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, not considered clinically significant by the Investigator, or the patient is lost to follow-up.

All AE identified, whether serious or non-serious, will be recorded in the AE eCRF beginning after the time of first administration of study drug in the double-blind period of the study and ending at the time of study completion or ET of the double-blind period or the OLE period, whichever is later. Serious adverse events considered related to screening procedures will be recorded in the AE eCRF starting on the date of informed consent. Whenever appropriate, the CTCAE (version 5.0 or most current version) should be utilized for naming common AE (Appendix 4).

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 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 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 AE 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 form (with a note stating signature is forthcoming). The Investigator **may change** their causality assessment based on follow-up information and submit an amended SAE report form.

All efforts will be made to obtain accurate and complete medical records for the SAE. All efforts to obtain information should be documented in the patient source documents.

The site will notify the IRB according to its guidelines.

The patient's condition will be followed by the Investigator or designated Subinvestigator until resolution of the condition or a return to baseline levels. If additional visits are required, the patient will be asked to return to the study site for further follow-up. If the condition is still ongoing at the time the patient exits the study, every effort will be made to continue to follow up with the patient for a reasonable period of time, as determined by the Investigator or until there is a return to baseline or stabilization of the condition. As additional information becomes available, such as hospital discharge notes and patient medical records, the Investigator will be notified and provided with all relevant information.

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

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

Serious AE 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 Day 225 (±3) or 84 (±3) days after last dose if patient does not enroll in the OLE period of the study, or until the start of the first dose in the OLE period of the study, unless otherwise directed by Allakos.

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. Female patients 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 subject) 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 AK002 will be reported as a SAE. If the patient received AK002, 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 AESI Reporting

Beginning from the time of first study drug infusion in the double-blind period of the study and ending at the time of study completion or ET of the double-blind period or the OLE period, whichever is later, unless otherwise directed by Allakos, any new AESI or new information related to a previously reported AESI must be recorded in the AE eCRF and designated as an "AE of special interest."

For patients participating in the OLE period, AESI will be assessed and recorded in the CRF of the AK002-021 double-blind treatment period database up until the start of the first open-label infusion after the Day 176 visit and recorded in the CRF of the AK002-021 OLE period database beginning from the start of the first open-label infusion after the Day 176 visit.

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 AE eCRF and designated as both "serious" and as an "AE 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. PPD should be contacted directly using the phone number and/or email address below to report medical concerns or for questions regarding safety.

Allakos AK002-021 Medical Monitor		**Allakos AK002-021 Backup Medical Monitor**	
PPD	MD	PPD	MD
Phone:	PPD	Phone:	PPD
Email:	PPD	Email:	PPD

13.9 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (iDMC) has been convened for this study. The iDMC will meet at established intervals (as per the iDMC Charter) throughout the study and will also convene as necessitated by data and/or safety reviews.

13.10 Study Withdrawal Criteria

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

- Occurrence of an exclusion criterion, which is clinically relevant and affects the patient's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor.
- Rebounding of eosinophil counts to >1500/μL in patients who entered the study with eosinophil levels >1500/μL, and whose eosinophil counts were initially suppressed after study drug will be withdrawn from the study at the instruction of the Safety Monitor.
- Serum transaminases (ALT and/or AST) >3 × ULN and total bilirubin >2 × ULN (confirmed by subsequent repeat) without an alternative explanation.
- Elevation of ALT or AST >3 × ULN (confirmed by repeat) with the appearance or worsening of symptoms felt by the Investigator to be potentially related to hepatic inflammation, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash.

13.11 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 trial is unjustifiable for medical or ethical reasons.
- Discontinuation of development 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 the Day 225 (±3) visit will be recorded as having completed the double-blind period of the study.

A patient who completes visits through the Day 176 (±3) visit and enters into the OLE period of the study will be categorized as having completed the double-blind period of the study.

A patient who completes visits through OLE Day 197 (Day 372) (±3) visit will be recorded as having completed the OLE period of 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 deviation requiring discontinuation of study treatment.
- Participation in any other study during the duration of this study.

- Use of a non-permitted concomitant drug which may adversely affect data interpretation in the opinion of the Medical Monitor.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration or 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 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 the 12-week follow-up period in Table 2, if possible (including follow-up EGD with colonoscopy).

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 statistical methods to be used for the analysis of the data from the study. A separate Statistical Analysis Plan (SAP), which must be documented as completed prior to unblinding the study, will describe data handling and statistical techniques in full detail and will supersede the statistical methods detailed in the protocol. The SAP will detail any modifications to the analysis plan described below.

Unless specified otherwise, baseline will be defined as the last 2 weeks of observation before the first intravenous infusion of the study drug. 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 proportion will be computed for categorical variables. Two-sided 95% confidence intervals will be provided for the mean and proportion. No formal statistical inferences will be made for safety parameters.

15.1 Sample Size

A total of approximately 80 patients will be enrolled.

First Co-Primary Endpoint: A sample size of 40 patients per treatment group will have >90% power to demonstrate a greater proportion of histologic responders at Week 24 in AK002 patients when compared to placebo patients, assuming the proportions of histologic responders are 0.6 and 0.1 in the AK002 and placebo groups, respectively.

Second Co-Primary Endpoint: A sample size of 40 patients per treatment group will provide 80% power to detect a statistically significant difference of 7.4 points between AK002 and placebo in the mean reduction from baseline in TSS at Weeks 23–24, assuming a common standard deviation of 12.5 points(AK002-003 data on file).

15.2 Analysis Populations

The Safety population is defined as all patients who are randomized and have received at least 1 infusion of the study drug.

The primary efficacy analysis population is the Evaluable population defined as all randomized patients who have received at least 1 infusion of the study drug and at study entry do not meet any of the following criteria:

1) >6 eosinophils/hpf in at least 1 esophageal biopsy at baseline.
2) Documented history of irritable bowel syndrome and baseline diarrhea intensity ≥3.

The complement to the Evaluable population will be referred to as the Excluded population. The Per Protocol (PP) population, defined as Evaluable population patients who have received at least 1 infusion of study drug and did not have significant protocol violations possibly interfering with assessment of efficacy. The Evaluable and Excluded populations will be used for all efficacy analysis. The PP population will be used for the primary endpoints and select secondary endpoint analyses. The Safety population will be used for all safety analysis.

The study statistician along with the study team will review protocol deviations to identify patients to be excluded from the PP analysis population.

15.3 Patient Disposition

Patient disposition and reason for early discontinuation will be tabulated. Patient demographics, baseline characteristics, and treatment exposure will be summarized.

15.4 Demographic and Baseline Characteristics

The following demographic and baseline variables will be summarized:

- Demographics
- Medical history
- Complete physical exam
- ECG at screening
- Screening vital signs and laboratory tests

Additionally, subgroup analysis will be conducted for the demographic variables (gender, race and age) and baseline disease characteristics (IgE <45 vs ≥ 45).

15.5 Study Drug Exposure

Number and percent (n and %) of subjects who have received 1, 2, 3, 4, 5, or 6 infusions will be presented.

15.6 Efficacy Analysis

15.6.1 Primary Efficacy Endpoint Analysis

The first co-primary endpoint will be analyzed using Fisher's exact test. Patients who experience an ICE, i.e., exit the study prematurely or initiate prohibited or restricted medication, prior to end of Week 24 will be treated as non-responders. Proportion of responders and the associated 95% confidence interval (CI) will be presented for each treatment group. The between-group difference and the associated 95% CI will also be computed and presented. Sensitivity analysis may be carried out using the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factor (baseline TSS <28 vs ≥28) to assess robustness of Fisher's exact test results.

The rationale for specifying Fisher's exact test for the primary analysis as opposed to specifying the CMH test is because when a stratum has 100% response for 1 treatment group and 0% response for another treatment group, the CMH test may lose efficiency or not be computable. This is evident from the Phase 2 study outcome.

The second co-primary endpoint will be analyzed using mixed model for repeat measures (MMRM) with treatment, week, treatment-by-week interaction, and baseline TSS-by-week interaction as fixed factors; gender and baseline TSS (continuous) as covariates; and study site (with pooling by geographic location) as random effect. If the model does not converge with pooled sites as a random effect, it will be simplified with pooled site as a fixed effect. Details about the method for pooling sites will be provided in the statistical analysis plan (SAP).

The weekly TSS is calculated as the average of the daily TSS. Weekly TSS will be set to missing if >3 daily TSS are missing. Baseline TSS will be the average of the last 2 weeks of daily TSS collected prior to the first infusion. The model variance-covariance matrix will be unstructured. However, if computation does not converge, the matrix will take the form of Toeplitz, autoregressive, or compound symmetry, whichever converges first.

Data on patients who experience an ICE, i.e., exit the study prematurely or initiate prohibited or restricted medications, prior to the end of Week 24 will be set to missing. If it is evident that the

second co-primary endpoint is confounded by the influence of background variables, then the second co-primary analysis will be conducted adjusting for the effects of the background variables. Possible confounding factors may include age, presence of esophageal inflammation, history of IBS, and presence of diarrhea at baseline.

Two sensitivity analyses are planned. The first is a pattern-mixture model, where it will be assumed that AK002 patients who experience an ICE will have a trajectory comparable to placebo post-ICE. This analysis will therefore provide a stress test of the missing at random (MAR) assumption of the MMRM employed in the principal analysis and will provide a conservative estimate of the treatment effect. The pattern-mixture model will be implemented using multiple imputations, and the inference of this sensitivity analysis will be based on the combined estimates using the standard multiple imputation technique. The imputed data sets will be analyzed with the same MMRM model utilized in the primary analysis and then summarized using PROC MIANALZE. The other is to analyze the average of Week 23 through Week 24 using ANCOVA with treatment and study site as factors, gender and baseline TSS (continuous) as covariates. Missing Week 23 through Week 24 weekly TSS will be imputed prior to ANCOVA using SAS PROC MI under the MAR assumption.

Detailed specifications for the missing data imputation will be provided in the SAP.

15.6.2 Secondary Efficacy Endpoint Analysis

If both tests of the co-primary endpoints are statistically significant, the hypothesis tests for the secondary endpoints will proceed sequentially in a prespecified order (see Section 4.2). If at any point, the statistical test is not significant at 2-sided α=0.05 level, the hypothesis testing procedure will stop. All endpoints prior to this point will be considered statistically significant, and inferential statistics after this point will be considered descriptive.

For tissue eosinophil count, the calculation will be based on the average count of the highest readings from the mucosa at baseline and Day 169 (Week 24). The change in tissue eosinophil count from baseline to Day 169 will be analyzed using ANCOVA with treatment, study site (with pooling by geographic location) as factors, and baseline eosinophil counts, gender, and baseline PRO TSS as covariates. Least square means (LSM), standard errors (SE), and 95% CI for individual treatment groups and LSM, SE, 95% CI, and p-value for the between-treatment difference will be presented.

Proportion of patients achieving mean eosinophil count of ≤1 cell/hpf in 3 highest duodenal hpf at Week 24 will be analyzed using Fisher's exact test like the analysis for the first co-primary endpoint.

Proportion of treatment responders at Weeks 23–24, where a responder is defined as >30% improvement in TSS and mean eosinophil count ≤15 cells/hpf in 3 highest duodenal hpf, will be analyzed using Fisher's exact test like the analysis for the first co-primary endpoint.

Proportion of patients with ≥50% reduction and ≥70% reduction in TSS from baseline to Weeks 23–24 will be analyzed using Fisher's exact test, and sensitivity analysis will be conducted using the CMH test stratified by the randomization stratification factors.

Change in weekly TSS will be analyzed using the MMRM model. The model will include fixed effects for baseline value, treatment, week, treatment by week interaction, baseline value by week interaction, and allow for random subject effects. The model variance-covariance matrix will be unstructured. However, if computation does not converge, the matrix will take the form of Toeplitz, AR(1), and compound symmetry, whichever converges first. The Kenward-Rogers approach for computing denominator degrees of freedom will be used to account appropriately for pooling of within-subject and between-subject variance estimates. LSM and the 95% CI for the between-group difference will be estimated for each week. The empirical cumulative distribution function (eCDF) and probability distribution function (PDF) plots will be presented for change from baseline TSS at Weeks 23–24.

15.6.3 Exploratory Analysis

Change from baseline CCI [redacted] at Week 25 will be analyzed using the CCI [redacted] similar to the analysis outlined above.

Change in CCI [redacted] as applicable, from baseline compared to post-treatment will be analyzed using the CCI [redacted] Changes in CCI [redacted] from baseline compared to post-treatment in the CCI [redacted] will be analyzed using the CCI [redacted]

Change from baseline in the CCI [redacted] will be summarized by CCI [redacted] for each of the following CCI [redacted]:

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

All [redacted] will be analyzed using the [redacted] as described above. [redacted] and the [redacted] for the between-group comparison will be presented for the [redacted] across Week 1 through Week 24 and for the [redacted] at each week.

- [redacted], the analysis variable, will be based on the [redacted] to establish a [redacted]
- [redacted] the analysis variable, will be the [redacted] (defined as [redacted] and calculated as the [redacted] to establish a [redacted].

They will then be analyzed using the [redacted]

15.7 Safety Analysis

Adverse Events: All AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA system organ class (SOC) 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.

15.7.1 Treatment Emergent Adverse Events

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

- Overview of TEAE to include
  - Number (%) of patients who reported at least 1 TEAE overall, by severity, and by relationship
  - Number (%) of patients who reported at least 1 serious TEAE
  - Number (%) of patients who reported at least 1 TEAE leading to treatment discontinuation
  - Number (%) of patients who reported at least 1 TEAE of special interest (TEAESI)
- TEAE by preferred term
- TEAE by SOC and preferred term
- TEAE by maximum severity, SOC, and preferred term
- TEAE by SOC and preferred term and relationship to study drug

- TEAE leading to withdrawal by SOC and preferred term
- Serious TEAE by SOC and preferred term
- TEAESI by SOC and preferred term

15.7.2 Anti-Drug Antibodies

Samples will be obtained for testing of ADA at times identified in Section 11.5.4.

15.7.3 Clinical Laboratory Assessments

Samples will be obtained for the clinical laboratory tests identified in Section 11.4, and laboratory tests to be summarized include chemistry, hematology, urinalysis, and AK002 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.

15.7.4 Vital Signs

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

15.7.5 ECG

Patient incidence of the Investigator's overall assessment (normal, abnormal – not clinically significant, and abnormal – clinically significant) will be summarized.

15.7.6 Physical Exam

New or worsening symptoms in the symptom-directed physical exams will be included in the by-patient data listing.

15.7.7 Concomitant Medications

All medications (prior and concomitant) will be coded using the most current World Health Organization Drug Dictionary (WHODD). Concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) Class and preferred term.

15.8 Patient Confidentiality

Patient identity should be confirmed, if possible, 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 or on social media.

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 the eCRF 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 handling and analysis of data will be conducted using good computing practices meeting Food and Drug Administration (FDA) guidelines for 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/Disclosure of Randomization Code

The database lock will occur after all subjects complete participation in the double-blind period of the study. For the database lock, applicable EDC data will be locked in order to protect write access after the following preconditions are fulfilled:

- All records are entered in the database.
- All AE are coded to the satisfaction of the Chief Medical Officer.

- All medications are coded to the satisfaction of the Chief Medical Officer.
- All data queries have been resolved.
- All decisions have been made regarding all protocol violations and ITT population exclusions.
- Written authorizations to lock the database are obtained from Allakos Clinical Data Management and the Chief Medical Officer.

The randomization code for this study will not be revealed until the previous preconditions are fulfilled, and documentation of the database lock is complete. After the database lock, the randomization code will be made available to individuals at Allakos who are involved in the data analysis. Data analysis will commence after the data lock. In addition, the PK and ADA data may be locked and assessed separately.

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
- Independent Ethics Committee (IEC)/IRB Documents
- Drug Accountability

- Correspondence
- Medical Reports
- Patient Data
- Monitoring Visit Reports
- Sample CRF and CRF Guidelines

16.7 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to 21 CFR Parts 50, 56, and 312 and ICH GCP Guideline E6. By signing this protocol, the Investigator grants permission to the Sponsor (or designee) and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. As necessitated by the COVID-19 pandemic, monitoring of all appropriate study documentation may occur off-site, with remote access to study documents, 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., 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 (IND) 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 Independent Ethics Committees/Institutional Review Boards

The protocol and ICF will be reviewed and approved by the IEC/IRB of each participating study site prior to study initiation. A Central IRB may be used if permitted by the participating study site. All SAE, regardless of causality, will be reported to the IRB in accordance with the SOP 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 SOP and policies of the IRB; new information that may adversely affect the safety of subjects 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.

In accordance with ICH GCP Guideline E6 Section 4.3.3, patients should be asked whether they would like their primary care physician notified of their study participation. If yes, the primary care physician should be notified in writing. Otherwise, the patient should sign a form stating that he/she does not wish to disclose such information.

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 subject 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 SOP and policies of the EGD facility/investigational site.

17.4 Publications

The preparation and submittal for publication of manuscripts containing the study results will 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 will comply with all applicable privacy laws including but not limited to the Health Insurance Portability and Accountability Act of 1996.

17.5 Clinical Trial Registration

This clinical study is registered on the Clinical Trial Registry Website, www.ClinicalTrials.gov, as NCT #04856891.

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. Beginning at dosing Day 1, Patients will be compensated for each completed week of daily questionnaires as long as at least 4 questionnaires per week are completed. After randomization, patients at participating study sites may be reimbursed for expenses associated with attending study visits. No additional compensation beyond what is stated in the ICF is permitted.

17.7 Investigator Responsibilities

By signing the Investigator Protocol Agreement page, 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 subjects.
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.

18. References

Alhmoud T, Hanson J, Parasher G. Eosinophilic gastroenteritis: an underdiagnosed condition. Dig Dis Sci, 2016;61:2585–92.

Allakos Clinical Study Report AK002-003. A Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability, and pharmacodynamic effect of AK002 in patients with eosinophilic gastritis and/or eosinophilic gastroenteritis, version 1, 18 June 2021.

Allakos Clinical Study AK002-019. A prospective study to identify the incidence of eosinophilic gastrointestinal diseases and elevated tissue mast cells among patients with chronic gastrointestinal symptoms. Data on file, 2021.

Bedell A, Taft T, Craven M, Guadagnoli L, Hirano I, Gonsalves N. Impact on health-related quality of life in adults with eosinophilic gastritis and gastroenteritis: A qualitative assessment. Dig Dis Sci, 2018;63:1148–57.

Bochner B. Siglec-8 on human eosinophils and mast cells, and Siglec-F on murine eosinophils, are functionally related inhibitory receptors. Clin Exp Allergy 2009;39(3):317-24.

Caldwell J, Collins M, Stucke E, Putnam P, Franciosi J, Kushner J, et al. Histologic eosinophilic gastritis is a systemic disorder associated with blood and extragastric eosinophilia, TH2 immunity, and a unique gastric transcriptome. J Allergy Clin Immunol 2014; 134:1114-24.

Dellon E, Peterson K, Murray J, Falk G, Gonsalves N, Chehade M, et al. Anti-Siglec-8 antibody for eosinophilic gastritis and duodenitis. N Engl J Med, 2020;383:1624–34.

Food and Drug Administration. Birth Control Chart from FDA.gov/consumers/free-publications-women/birth-control. FDA.gov/consumers/free-publications-women/birth-control, 21 Jun 2021, retrieved 27 Feb 2022, from https://www.fda.gov/consumers/free-publications-women/birth-control.

Food and Drug Administration. Guidance for industry ICH E9 (R1) statistical principles for clinical trials addendum: estimands and sensitivity analysis in clinical trials. CDER, May 2021.

Hudson S, Herrmann H, Du J, Cox P, Haddad el B, Butler B, et al. Developmental, malignancy-related, and cross-species analysis of eosinophil, mast cell, and basophil siglec-8 expression. J Clin Immunol, 2011;31:1045–53.

Jensen E, Martin C, Kappelman M, Dellon E. Prevalence of eosinophilic gastritis, gastroenteritis, and colitis: Estimates from a national administrative database. J Pediatr Gastroenterol Nutr, 2016;62:36–42.

Katz P, Gerson L, Vela M. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol, 2013;108:308–328.

Licari A, Votto M, Scudeller L, De Silvestri A, Rebuffi C, Cianferoni A, Marseglia G. Epidemiology of nonesophageal gastrointestinal diseases in symptomatic patients: A systematic review and meta-analysis. J Allergy Clin Immunol Pract, 2020;8:1994–2003.

López-Medina G, Gallo M, Prado A, Vicuna-Honorato I, Díaz de León R. Eosinophilic gastroenteritis: case report and review in search for diagnostic key points. Case Rep Gastrointest Medicine, 2015; 239506:1–5.

Mansoor E, Saleh M, Cooper G. Prevalence of eosinophilic gastroenteritis and colitis in a population-based study, from 2012-2017. Clin Gastroenterol Hepatol, 2017; 15:1733-41.

Peterson K, Byrne K, Vinson L, et al. Elemental diet induces histologic response in eosinophilic esophagitis. Am J Gastroenterol, 2013;108:759–66.

Prussin C. Eosinophilic gastroenteritis and related eosinophilic disorders. Gastroenterol Clin North Am 2014; 43: 317-27.

Reed C, Woosley J, Dellon E. Clinical characteristics, treatment outcomes and resource utilization in children and adults with eosinophilic gastroenteritis. Dig Liver Dis 2015; 47: 197-201.

Sampson H, Munoz-Furlong A, Campbell R, Adkinson Jr N, Bock S, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117(2):391–7.

Wechsler J, Schwartz S, Amsden K, Kagalwalla A. Elimination diets in the management of eosinophilic esophagitis. J Asthma Allergy, 2014;7:85–94.

Zhang M, Li Y. Eosinophilic gastroenteritis: A state-of-the-art review. J Gastroenterol Hepatol 2017; 32: 64-72.

19. Appendices

19.1 Appendix 1: 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.

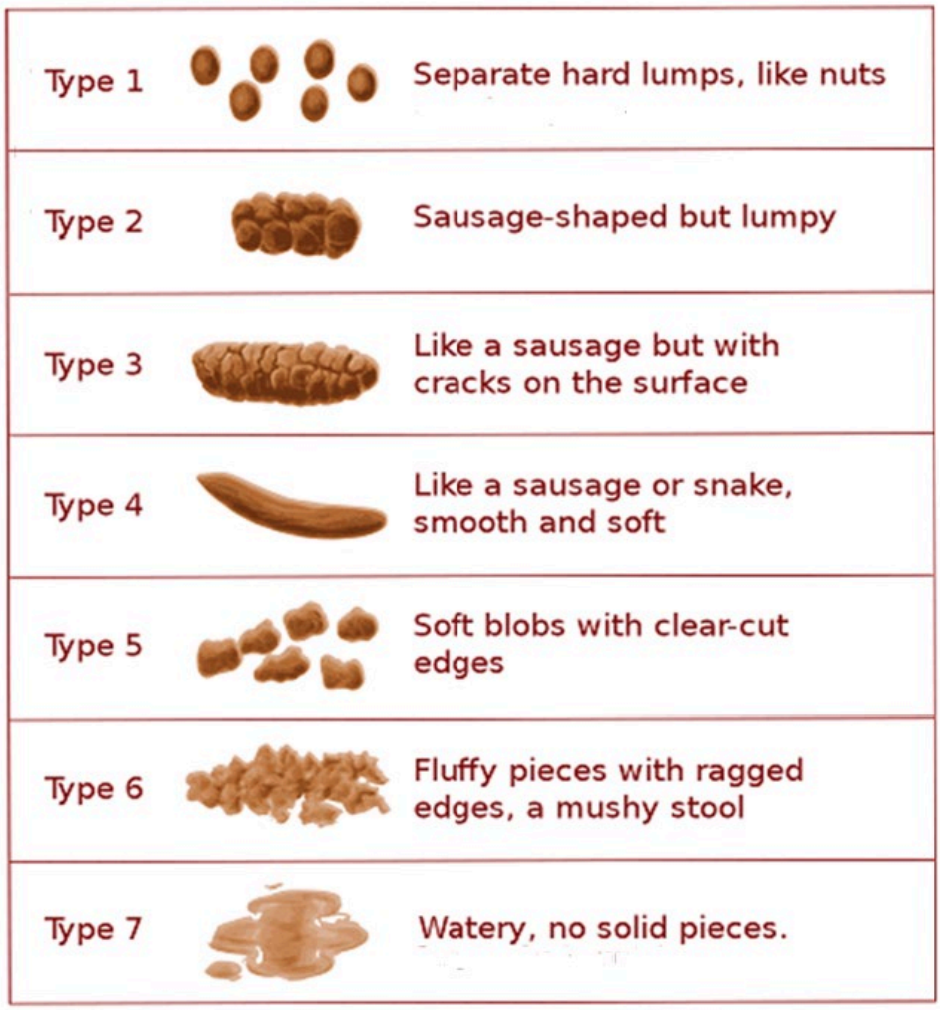
1. Over the past 24 hours, please rate the intensity of your **abdominal (stomach) pain** at its worst.	0 ☐ NO ABDOMINAL PAIN	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐ WORST POSSIBLE ABDOMINAL PAIN
2. Over the past 24 hours, please rate the intensity of your **nausea (feeling like you have to throw up)** 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

19.1 Appendix 1: PRO Questionnaire cont.

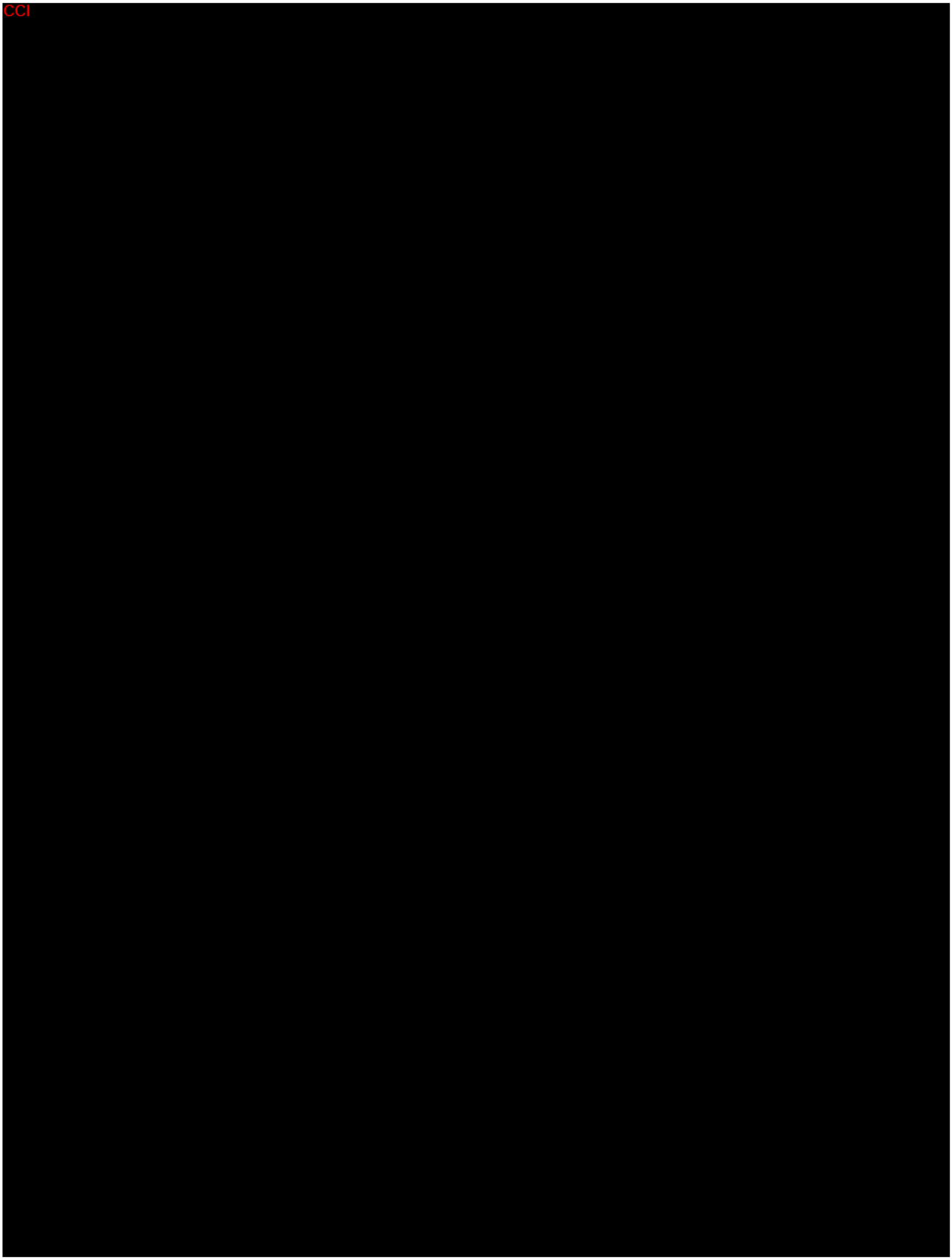
8. Over the past 24 hours, please rate the intensity of your **bloating (stomach feels bigger or under pressure)** at its worst.	0 ☐ NO BLOATING 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ WORST POSSIBLE BLOATING
9. Over the past 24 hours, how many times did you have diarrhea (defined as **type 6 or 7 stools** 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

19.1 Appendix 1: PRO Questionnaire cont.

Bristol Stool Form Scale (English for United States)



BSFS – United States/English – Original version. BSFS_AU1.2_eng-USori.doc


CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

Thank you for completing these questions!

CCI

19.3 Appendix 3: Baseline Diet Assessment

Instructions: To be completed by Study Personnel, through direct interview with Study Participant. Please ask questions to Study Participants, much as they appear below. This assessment should be conducted on Day 1 of screening. This assessment asks about symptoms of eosinophilic duodenitis (EoD).

1. Are you on Specific, Doctor-Prescribed Diet? Yes ☐ No ☐

If Yes, what is the diet?

☐ Elemental [If ticked-enteral/tube feeding?] Yes ☐ No ☐

☐ 6-food or 3 Food Elimination Diet

☐ Supplemental Protein Shake/drink specify: _____

☐ Other; describe: _____

2. Do you have any <u>confirmed</u> food allergies (i.e., confirmed by skin-prick testing or blood tests)? Yes ☐ No ☐

If Yes, what are they? _____

_____

3. Does eating certain foods seem to make your EoD symptoms <u>worse</u>? Yes ☐ No ☐

If Yes, what are the 3 specific foods/types of foods that make the effects worse?

Food or Type of Food	Effect

4. Do you avoid eating any specific foods or types of foods due to your EoD symptoms? Yes ☐ No ☐

If Yes, which foods are **always** avoided? _____

_____

5. Do you avoid? (tick all that are appropriate)

☐ Milk ☐ Egg ☐ Wheat ☐ Soy

What are the main foods that YOU DO eat?

If a full diet is eaten do not list all types of foods, just write "All foods."

_____

6. Do you avoid eating at certain times of the day to avoid symptoms of EoD? Yes ☐ No ☐

If Yes, please describe: _____

_____

19.4 Appendix 4: 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 g/dL	Increase in >2–4 g/dL	Increase in >4 g/dL	-	-
Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin above normal.					
Lipase increased	>ULN –1.5 × ULN	>1.5–2.0 × ULN; >2.0-5.0 × ULN and asymptomatic	>2.0–5.0 × ULN with signs or symptoms; >5.0 × ULN and asymptomatic	>5.0 × ULN and with signs or symptoms	–
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.					

19.5 Appendix 5: EGD and Colonoscopy Histology

Details for collecting, labeling, and shipping specimens will be provided separately in the 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

  For patients with a history of EoE and/or with a score of ≥3 on the dysphagia question during screening, esophageal biopsies will also be collected at screening and postdose.

- Stomach: 1) H&E; 2) tryptase
- Duodenum: 1) H&E; 2) tryptase
- Colon: 1) H&E; 2) tryptase

Biopsies will be obtained from the following:

- **Esophagus** (if patient has a history of concomitant EoE, if esophagus looks suspicious for EoE, or if patient is symptomatic on screening dysphagia question, quantified by a score of >3 on the dysphagia question on at least 1 day during screening).
  - 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.

  A count of ≥15 eosinophils/hpf in at least 1 esophageal site will be considered diagnostic of EoE for the purposes of the study.

- **Stomach**
  - 4 specimens from separate areas of the gastric antrum (2–5 cm proximal to the pylorus)
  - 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.
  - 1 fragment will be collected for exploratory analysis (shipped to Allakos directly).

19.5 Appendix 5: EGD and Colonoscopy Histology cont.

- **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.
  - 1 fragment will be collected for exploratory analysis (shipped to Allakos directly).
- **Colon**
  - At least 2 fragments (preferably 3 fragments) each from terminal ileum; ascending, transverse, descending, and sigmoid colon; and rectum
  - Up to 2 extra specimens may be collected if there are any additional areas of interest.
  - 1 fragment each will be collected from terminal ileum; ascending, transverse, descending, and sigmoid colon; and rectum for exploratory analysis (shipped to Allakos directly).

The following will be reported for esophageal biopsies:

- Maximum number of eosinophils/hpf
- Maximum number of tryptase-positive mast cells/hpf

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:

- A highly sensitive monoclonal immunohistochemical stain will be used. The following histopathologic parameters will be graded using the Updated Sydney System from 0 (absent) to 3 (marked or severe):
  - Active inflammation
  - Chronic inflammation

19.5 Appendix 5: EGD and Colonoscopy Histology cont.

  - Intestinal metaplasia
  - Atrophy
  - Reactive gastropathy
- Eosinophil and mast cell counts will be reported as:
  - Maximum number of eosinophils/hpf in at least 5 hpf on each biopsy fragment
  - Maximum number of tryptase-positive mast cells/hpf in at least 5 hpf on each biopsy fragment

The following will be reported for duodenal biopsies:

- Eosinophil and mast cell counts will be reported as:
  - Maximum number of eosinophils/hpf in at least 3 hpf on each biopsy fragment
  - Maximum number of tryptase-positive mast cells/hpf in at least 3 hpf on each biopsy fragment
- Duodenal intraepithelial lymphocytosis (with counts per 100 enterocytes when count is >20)
- Villous architecture

The following will be reported for ileal and colonic biopsies:

- Eosinophil and mast cell counts will be reported as:
  - Maximum number of eosinophils/hpf in at least 5 hpf on each biopsy fragment
  - Maximum number of tryptase-positive mast cells/hpf in at least 5 hpf on each biopsy fragment
- In addition, the ileal and colonic biopsies will be evaluated for chronic or active inflammation, lymphocytic colitis, collagenous colitis, or evidence of inflammatory bowel disease. The presence of any of these abnormalities will be reported by the central reader and evaluated against eligibility criteria by the Investigator and Allakos Medical Monitor.

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

19.6 Appendix 6: Sampson's Criteria of Anaphylaxis

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

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

OR

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

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

19.7 Appendix 7: ePRO Teaching Tool for Study AK002-021

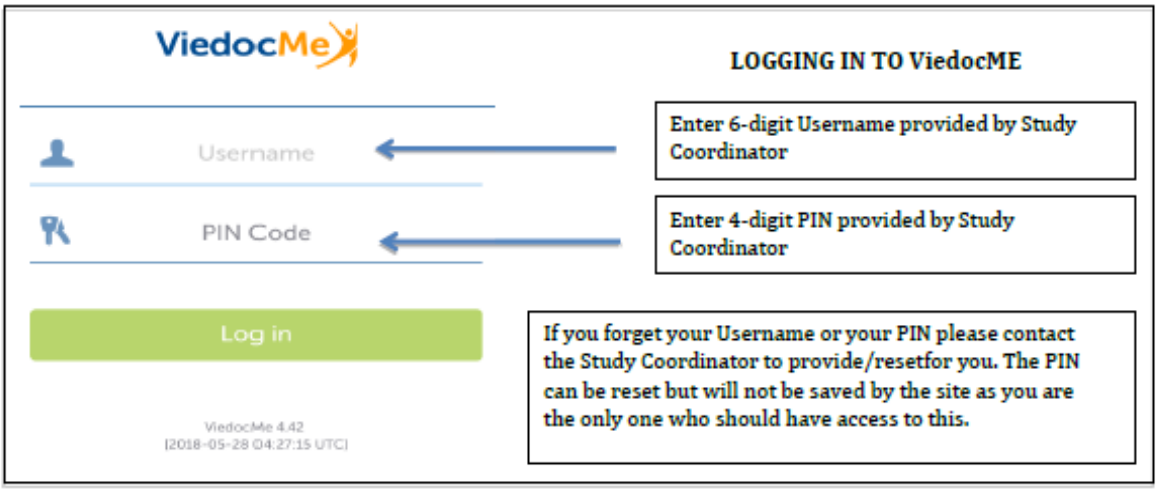
INSTRUCTIONS FOR COMPLETION OF ELECTRONIC QUESTIONNAIRES

You are being asked to complete a ONCE DAILY 10-question EG/EoD questionnaire about your current symptoms, as well as other questionnaires as specified on page 3.

WEBSITE: https://v4me.viedoc.net

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 not be available for completion at a later time. 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 entire duration of the study, you will answer the EG/EoD PRO questionnaire and one additional question each, for "Dysphagia" and "Constipation".



REMINDERS FROM ViedocME FOR COMPLETION OF DAILY QUESTIONNAIRES

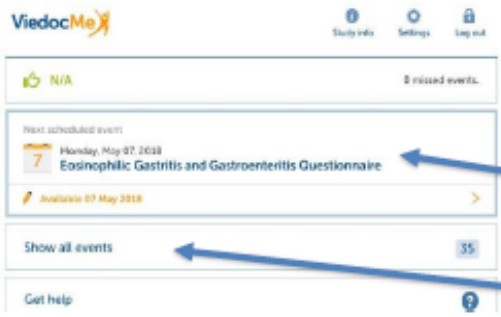
- When the Study Coordinator sets up your ViedocME account you can choose to receive a DAILY reminder to complete your questionnaire(s) for the day. The reminder(s) will be sent if you diary entry has not been completed by 8PM each evening (in your study site time zone).
- The ViedocME reminders can 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.*

Version 11 May 2021 **Page 1 of 4**

Appendix 7: ePRO Teaching Tool cont.

THINGS TO REMEMBER WHEN USING THE ELECTRONIC 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 PRO 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 first questionnaire has been submitted. These questions will NOT be visible prior to the previous questionnaire being submitted/SENT for that day.

- You will daily complete one additional question each, about dysphagia (difficulty swallowing) and constipation following the completion of the 10 question ePRO questionnaire.
- On study visit days you will access ViedocME to complete the SF-36 Health Survey.
- On screening Day 19 and study days 7, 28, 225 and ET, you will complete the 1-question PGIS via ViedocME.
- On study days 7, 28, 225, and ET, you will complete the 1-question PGIC via ViedocME.

COMPLETING THE DAILY QUESTIONNAIRES DURING THE STUDY

You will complete the EG/EoD questionnaire, and the additional questions during the entire duration 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 received all study drug or at the last study visit)

During the screening period, the questionnaire is used to determine if your symptoms are appropriate in type and intensity to be enrolled into the study.

Patients with a history of EoE and/or with a score of ≥3 on the dysphagia question during screening will also have esophageal biopsies collected during the EGD at screening and postdose.

You will start completing the daily questionnaires (EG/EoD daily questionnaire, and the additional questions) on the first day of your participation in this study and will complete the questionnaires until your last day of participation in this study.

Version 11 May 2021 Page 2 of 4

Appendix 7: ePRO Teaching Tool cont.

ePRO Teaching Tool: Study AK002-021 (continued)

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

Username: _____

PIN (do not share with others): _____

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

QUESTIONNAIRE	Screening	During Study
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	Screening	During study
Dysphagia question	X	X
Constipation question	X	X

*Additional questions for dysphagia and constipation will populate only AFTER you have completed the daily EG/EoD questionnaire.

You must hit SEND and GO TO START PAGE to see all questionnaires.

START DIARY TODAY!

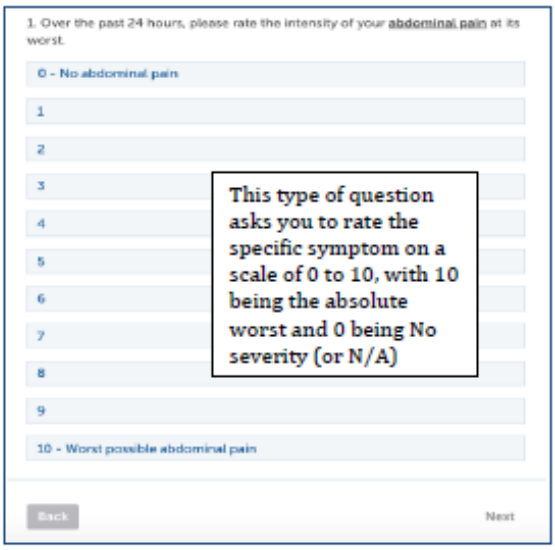
Additional Information regarding diary completion on Page 4

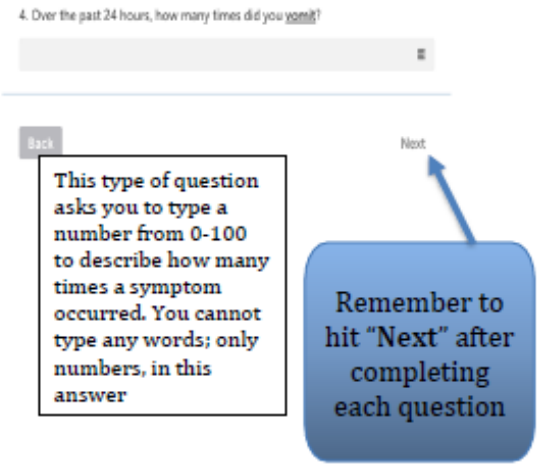
Appendix 7: ePRO Teaching Tool cont.

ePRO Teaching Tool: Study AK002-021 (continued)

TYPES OF QUESTIONS ON EG/EoD QUESTIONNAIRE

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





How to answer ViedocME questions

- Response to 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 with a questionnaire. All questions must be answered.
- Answer each question the best 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 9:00PM Tuesday night to 8:59PM on Wednesday night.
- Vomiting occurs from 9-10PM Wednesday night. Vomiting will be captured on the next day's diary (Thursday night's diary).

WHAT TO DO IF YOU WILL BE WITHOUT INTERNET ACCESS

- Use one copy of the paper questionnaire provided at screening 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 the study coordinator as soon as possible.

Version 11 May 2021 Page 4 of 4

CCI

[redacted]

CCI

19.10 Appendix 10: Additional Questions for Dysphagia and Constipation

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 these every day, at approximately the same time.*

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

Answer this question unless instructed to stop.

Question # 1: Over the past 24 hours, please rate the Intensity of your **difficulty swallowing (dysphagia**) at its worst.

- ☐ 0 – No swallowing difficulty
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8
- ☐ 9
- ☐ 10 – Worst possible swallowing difficulty

Answer this question unless instructed to stop.

Question # 2: Over the past 24 hours, please rate the intensity of your **constipation (difficulty passing stool)** at its worst.

- ☐ 0 – No constipation
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8
- ☐ 9
- ☐ 10 – Worst possible constipation

Version 06-JAN-2021 Page 1 of 1

19.11 Appendix 11: Previous Treatments and Procedure Review

Instructions: To be completed by Study Personnel through direct interview with Study Participant. Please ask questions to Study Participants, much as they appear below. This review should be conducted anytime during the screening period.

1. **Were you clinically diagnosed with EoD (sometimes called EGE) before participating in this study?**
   Yes ☐ No ☐

2. **Have you previously taken prescription medications specifically for the diagnosis of EoD?**
   N/A, not previously diagnosed with EoD ☐ Yes* ☐ No ☐
   If yes* please list: _____
   All medications taken for EoD or EoD symptoms at any time should be listed on the ConMed Log.

3. **Have you previously taken over-the-counter (OTC) medications for symptoms of EoD (i.e., Zantac®, Tylenol®, Tums®)?** Yes* ☐ No ☐
   If yes* please list: _____
   All medications taken for EoD symptoms at any time should be listed on the Con-Med Log.

4. **Have you previously tried changing your diet to help improve the symptoms of EoD?** Yes* ☐ No ☐
   If yes* please describe: _____

5. **Have you previously tried changing your eating habits to help improve the symptoms of EoD?**
   Yes* ☐ No ☐
   If yes*please describe: _____

6. **Have you previously tried other methods to help improve the symptoms of EoD (i.e., acupuncture, pressure point therapy)?** Yes* ☐ No ☐
   If yes* please describe: _____

7. **How many EGD and/or colonoscopies have you had in the last 5 years?**
   EGD: _____ Colonoscopy: _____

8. **What was the date of the last EGD/colonoscopy prior to screening for this study?**
   EGD: ____/____/____ Colonoscopy: ____/____/____
   DD / MM / Year DD / MM / Year

Additional Comments

_____

_____ _____
Name of Person completing Previous Treatments and Procedure Review Date

19.12 Appendix 12: Hepatitis B and Hepatitis C Serologic Testing Details

19.12.1 Hepatitis B Testing Details

HBsAg positive patients are excluded. However, in case of past infections/vaccinations in order to qualify, the patient's testing status needs to align with the information in Table 6.

Table 6 Hepatitis B Testing

Past Infection (Resolved)			**Vaccinated**	
HBsAg	Negative	***Or***	HBsAg	Negative
Anti-HBc	Positive		Anti-HBc	Negative
Anti-HBs	Positive		Anti-HBs	Positive

19.12.2 Hepatitis C Testing Details

Anti-HCV positive and HCV-RNA positive are excluded. In order to qualify for enrollment, the patient's testing status needs to align with the information in Table 7.

Table 7 Hepatitis C Testing

Non-Reactive			**Past Infection (Resolved)**	
Anti- HCV	Negative	***Or***	Anti- HCV	Positive
			HCV RNA	Negative

19.13 Appendix 13: Open-Label Extension Period – Optional

19.13.1 Summary of the Open-Label Extended Dosing Period

Patients who receive all 6 infusions of study drug (AK002 or placebo), complete study visits through Day 176 (±3) of the double-blind treatment period and meet extended dosing eligibility criteria will be given the option to receive 6 doses of AK002 through the Open-Label Extended Dosing (OLE) period.

Patients will follow the visits and procedures of the double-blind period of the study until starting the OLE period of the study. At least 1 day after Day 176 (±3), eligible patients participating in the OLE period will begin following the OLE Schedule of Assessments (Table 8) and will no longer follow the double-blind period of the study Schedule of Assessments (Table 2). It is important that the first dose of the OLE period is started ***after*** Day 176 to allow the patient to receive prednisone premedication 12–24 hours prior to the first dose of AK002 in the OLE period. The extended dosing period is summarized as follows:

- The Investigator will evaluate whether the patient is eligible for OLE. If eligible, the patient will be given the option to participate in the OLE period and receive 6 doses of open-label AK002.
- On OLE Dose 1, eligible patients who completed all double-blind Day 176 required procedures will be instructed to begin following the OLE Schedule of Assessments (Table 8).
- All patients will receive 80 mg oral prednisone 12–24 hours prior to the first infusion in the OLE period. 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.
- OLE patients will receive 6 doses of open-label AK002 (OLE Days 1, 29, 57, 85, 113, and 141). All open-label AK002 infusions will be given at a dose of 3 mg/kg.
- Patients will remain at the site for at least 1 hour of observation after each dose. In the event of an IRR, the patient may require prolonged observation (>1 hour or until the symptoms resolve) as per the Investigator's discretion.
- Patients will be followed for approximately 8 weeks after last dose. Follow-up visits will occur on Day 344 (±7) and Day 372 (±7) (OLE Day 169 and OLE Day 197, respectively).
- If absolute lymphocyte and/or eosinophil counts have not recovered by the OLE Day 197 visit, patients will return approximately every 28 days for extended follow-up until counts have recovered.

19.13.2 OLE Objective

The objective of the OLE period is to evaluate long-term safety and tolerability of up to 6 doses of open-label AK002. The Medical Monitor will review OLE period data relating to safety and tolerability throughout the course of OLE dosing.

19.13.3 OLE Eligibility Criteria

Following completion of the randomized, double-blind, placebo-controlled treatment (all 6 doses) and the Day 176 visit, eligible patients will have the option to receive 6 doses of open-label AK002 through participation in the OLE period.

Patients who are not eligible for OLE or who choose not to participate in the OLE period will continue to follow the study Schedule of Assessments for the double-blind period of the study (Table 2).

19.13.3.1 OLE Inclusion Criteria

Patients are eligible to participate in the OLE period if all of the following criteria are met:

1) Patient completed the randomized, double-blind, placebo-controlled treatment period, defined as having received all 6 infusions of study drug (AK002 or placebo) and completed the Day 176 visit.
2) Patient is willing and able to comply with the OLE period Schedule of Assessments (Table 8), including receiving the first open-label AK002 infusion at least 1 day after the Day 176 (±3) visit.

19.13.3.2 OLE Exclusion Criteria

Patients are not permitted to participate in the OLE period if any of the following criteria are met:

1) Previous administration of the study drug (AK002 or placebo) was poorly tolerated by the patient, in the opinion of the Investigator.
2) Any other reason that in the opinion of the Investigator or Medical Monitor makes the patient unsuitable for participation in the OLE period.

19.13.4 OLE Treatment

Formulation, storage, preparation, and administration of the open-label AK002 drug product for OLE will be consistent with Section 9. Study Treatment of this protocol and the AK002-021 Pharmacy Manual.

Twelve to 24 hours prior to the first open-label AK002 infusion only, all patients will receive 80 mg oral prednisone. An approved alternative(s) may be used with the approval of the Medical Monitor. This dose of prednisone premedication should be recorded in the Concomitant Medications CRF of both the AK002-021 double-blind treatment period database and the AK002-021 OLE period database. Premedication may be administered prior to subsequent infusions at the Investigator's discretion, but only with written approval from the Medical Monitor.

The first OLE infusion of AK002 will be administered at a dose of 3 mg/kg over at least 4 hours after Day 176 (±3). The subsequent infusions on OLE Days 29, 57, 85, 113, and 141 (±3), depending on the patient's tolerance per the Infusion Rate Schedules in the AK002-021 Pharmacy Manual can be given over ≥1 hour. Any reduction in infusion rate due to tolerability will not be considered a deviation from the protocol. If the infusion is slowed or interrupted, the infusion must be completed within 8 hours of preparation (prior to expiry).

The patient will be observed for at least 1 hour (or more as per the Investigator's discretion) after the end of all infusions. In the event of an IRR, the patient may require prolonged observation (>1 hour or until the symptoms resolve), as per the Investigator's discretion. Patients will also be instructed to immediately contact the study doctor if any reactions occur after discharge.

19.13.5 OLE Procedures and Guidelines

Apart from differences in the Schedule of Assessments beginning after double-blind Day 176 (±3), the OLE period of the study will be conducted in accordance with the protocol. This includes prohibited medications, dietary and lifestyle restrictions, AK002 preparation and administration, study assessment and procedure guidelines including the EGD and colonoscopy with biopsy, AE reporting, withdrawal criteria and stopping rules, data collection and management, and ethical and regulatory requirements.

The Investigator will evaluate whether the patient is eligible for the OLE period. After completion of procedures on Day 176 (±3), eligible patients that choose to participate in the OLE period will begin following the OLE Schedule of Assessments (Table 8) and will receive the first open-label AK002 infusion.

Table 8 Study AK002-021 Schedule of Assessments: Open-Label Extension Period

Assessment Description	Screening	Open-Label Extended Dosing (20 weeks)						OLE Follow-Up (≥8 weeks)[22]	
	No Visit[2]	OLE Dose 1 Day 176 [OLE Day 1] (±3 days)	OLE Dose 2 Day 204 [OLE Day 29] (±3 days)	OLE Dose 3 Day 232 [OLE Day 57] (±3 days)	OLE Dose 4 Day 260 [OLE Day 85] (±3 days)	OLE Dose 5 Day 288 [OLE Day 113] (±3 days)	OLE Dose 6 Day 316 [OLE Day 141] (±3 days)	Day 344 [OLE Day 169] (±3 days)	Day 372 [OLE Day 197] (±7 days) or ET[21]
Evaluate Eligibility for OLE Period[2]	X[2]	X[2]							
CCI		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X
Baseline Diet Compliance[4]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X
Weight and Vital Signs[5,6]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X
Total Serum IgE[7,8]							X[1]		X
Complete Blood Count with Differential[7,9]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X
Chemistry[7,10]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X
Pharmacokinetics[7,11]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X
Anti-drug Antibodies[7,12]		X[1]	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X
Urinalysis[7,13]		X[1]	X[1]						X
Urine Pregnancy Test[7,14]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]		
Premedication: Prednisone[15]	X								
Access IRT: IP Kit Assignment		X	X	X	X	X	X		
AK002 Administration[16]		X	X	X	X	X	X		
Post-Dose Observation Period[17]		X	X	X	X	X	X		
ePRO Questionnaire (will include Additional Questions)[23]	<----------Complete electronically one time daily---------->								
Symptom-Directed Physical Exam[18]		X	X	X	X	X	X	X	X
EGD and Colonoscopy with Biopsy Collection[19]								X	
Concomitant Medications		X	X	X	X	X	X	X	X
Adverse Events[20]		X	X	X	X	X	X	X	X

ADA:	Anti-AK002 antibody	ET:	Early Termination	IRT:	Interactive Response Technology
CBC:	Complete blood count	FSH:	Follicle-stimulating hormone	CCI	[redacted]
ECG:	Electrocardiogram	hCG:	Human Chorionic Gonadotropin	CCI	[redacted]
ePRO:	electronic Patient Reported Outcome	IP:	Investigational Product	PK:	Pharmacokinetics

Table 8 Notes

1) Refer to assessment table note number for specific timing (e.g., predose, during infusion, postdose).
2) The Investigator will evaluate whether the patient is eligible for the OLE period per Section 19.13.3. Immediately after the double-blind Day 176 (±3) assessments, eligible patients that choose to participate in the OLE period will begin following the OLE Schedule of Assessments and will receive the first open-label AK002 infusion. Prednisone premedication will be administered after the double-blind Day 176 assessments are completed.
3) CCI [redacted] should be the first assessment completed by the patient at the beginning of the study visit prior to other assessments.
4) Patients should maintain the baseline diet consistently throughout the study. Diet compliance will be discussed during study visits and any variance will be documented.
5) Weight will be measured predose on all OLE dosing days, Day 344, and Day 372 or ET.
6) On all OLE dosing days, vital signs will be measured within 30 minutes predose, 15 (±5) minutes after infusion start, within 15 minutes following the end of infusion and just prior to discharge. Patient should be at rest for ≥5 minutes before vital signs (systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate) are measured.
7) Refer to the Laboratory Manual for collection, processing, and shipment instructions. Samples should be shipped on the same day as collection.
8) Blood for total serum IgE will be obtained predose on OLE Dose 6 (Day 316) and again on Day 372 or ET.
9) Blood for CBC with differential will be obtained at all OLE period study visits. On OLE dosing days the blood sample will be drawn just prior to each infusion and 1 hour (±15 minutes) after the end of each infusion.
10) Blood for chemistry will be obtained at all OLE period study visits. On OLE dosing days blood for chemistry will be drawn predose.
11) Blood for PK will be obtained at all OLE period study visits. On OLE dosing days blood for PK will be drawn predose.
12) Blood for ADA will be obtained predose on OLE Dose 1 and on Day 372 or ET. For OLE Doses 2, 3, 4, 5 and 6, blood for ADA will be obtained only if a suspected immunogenicity-related AE occurs.
13) Urine for urinalysis will be obtained predose on OLE Dose 1, OLE Dose 2, and Day 372.
14) For females of childbearing potential, urine will be collected, tested, and pregnancy result confirmed predose on all dosing days.
15) 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. This dose of prednisone premedication prior to the first infusion must be administered ***after*** all double-blind Day 176 assessments are performed and should be recorded in the Concomitant Medications CRF of both the AK002-021 double-blind treatment period database and the AK002-021 OLE period database.

Table 8 Notes cont.

16) Open-label AK002 will be administered as a single peripheral intravenous infusion over at least 4 hours on OLE Dose 1 and over at least 1 hour on subsequent dosing days. Refer to the AK002-021 Pharmacy Manual for detailed administration and infusion rate schedule instructions.

17) Patients will remain under observation at the site for at least 1 hour after the end of each infusion. In the event of an IRR, the patient may require prolonged observation (>1 hour or until the symptoms resolve), as per the Investigator's discretion. Patients will also be instructed to immediately contact the study doctor if any reactions occur after discharge.

18) If a new or worsening symptom (or clinically significant finding) is observed or reported, the Investigator or designee will determine whether a symptom-directed physical examination is warranted and should perform it at any time or multiple times during a visit (predose, during infusion, and/or postdose).

19) An EGD and colonoscopy with biopsy collection will be performed on Day 344 (±3) or 28 (±3) days after last dose of study drug if ET. The EGD and colonoscopy should take place on the same day. EGD and colonoscopy biopsies will be collected, processed, and shipped in accordance with Section 11.2.4, Appendix 5, and the Histology Manual. The patient should arrive fasting for the EGD and colonoscopy procedures, as specified by instructions form the EGD provider, and all concomitant medications provided to the patient prior to or during EGD and colonoscopy procedures should be captured in the source data and electronic CRF.

20) All AE, including AESI and SAE, will be captured throughout the entire OLE period until Day 372 or ET. Adverse events will be assessed and recorded in the CRF of the AK002-021 OLE period database beginning from the start of the first open-label infusion during the OLE Dose 1 visit.

21) ET visits should be conducted 28 (±3) days after last dose of open-label AK002 or prior to this, if necessary, to ensure compliance with the visit. If a patient discontinues the study >28 days after last dose of study drug, the ET visit should be conducted as soon as possible.

22) If absolute lymphocyte and/or eosinophil counts do not recover (to normal range or baseline levels) by Day 372 or ET, extended follow-up visits are required every 28 (±3) days thereafter to monitor blood counts until they recover. Extended follow-up visits consist of blood collection for CBC with differential and collection of AESI and SAE.

23) Patients entering into the OLE period of the study should continue completing the PRO daily. The PRO should be completed around the same time each day. Patients should continue completing the additional questions that they were completing during the double-blind period of the study.