A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AK002 in Adult and Adolescent Subjects with Active Eosinophilic Esophagitis

NCT Number: NCT04322708
Document Date: 28 Oct 2021
IRB Approval Date: 05 Nov 2021

975 Island Drive, Suite 201, Redwood City, CA 94065

Clinical Research Protocol AK002-014

A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AK002 in Adult and Adolescent Subjects with Active Eosinophilic Esophagitis

Protocol Number	AK002-014
Version and Date	Original 16 October 2019 Amendment 1 13 January 2020 Amendment 2 07 May 2020 Amendment 3 08 July 2020 Amendment 4 20 August 2020 Amendment 5 07 May 2021 **Amendment 6 28 October 2021**
Investigational Product	AK002
Study Phase	2/3
Sponsor	Allakos Inc., 975 Island Drive, Suite 201, Redwood City, CA 94065 USA
Medical Monitor	Primary: PPD MD Telephone: PPD Email: PPD Backup: PPD MD Telephone: PPD Email: PPD

Approval: PPD

PPD MD, MBA

28-Oct-2021 | 11:02 PDT

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 subjects 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: AK002-014

IND: 143997

Protocol Title: A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AK002 in Adult and Adolescent Subjects with Active Eosinophilic Esophagitis

Original Protocol: 16 October 2019

Amendment 1: 13 January 2020

Amendment 2: 07 May 2020

Amendment 3: 08 July 2020

Amendment 4: 20 August 2020

Amendment 5: 07 May 2021

Amendment 6: **28 October 2021**

Investigator Printed Name: _____

Signature: _____

Date: _____

Table of Contents

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 events
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
ANCOVA	Analysis of covariance
Anti-IL-5	Anti-interleukin-5
AST	Aspartate aminotransferase
BMI	Body mass index
C	Centigrade
CBC	Complete blood count
CFR	Code of Federal Regulation
CI	Confidence interval(s)
cm	Centimeter
CTCAE	Common Terminology Criteria for Adverse Events
CU	Chronic Urticaria
DSQ	Dysphagia Symptom Questionnaire
EC	Eosinophilic colitis
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
ELISA	Enzyme-linked immunosorbent assay
EoE	Eosinophilic esophagitis
EoD	Eosinophilic duodenitis
CCI	[redacted]

EREFS	Eosinophilic Esophagitis Reference Score for Endoscopic Abnormalities
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
hpf	High power field
ICE	Intercurrent event(s)
ICF	Informed consent form
ICH	International Conference on Harmonisation
iDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IgG1	Immunoglobulin G1
IND	Investigational New Drug
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
ISM	Indolent systemic mastocytosis
IRT	Interactive Response Technology
ITIM	Immunoreceptor Tyrosine-based inhibitory motif
IV	Intravenous
JAK	Janus kinase (inhibitors)
kg	Kilogram
L	Liter
LSM	Least squares means
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Multiple imputation
MITT	Modified Intent-to-Treat (population)
mM	Millimolar
mL	Milliliter

MMRM	Mixed effects model for repeated measures
MNAR	Missing not at random
MTD	Maximum tolerated dose
NaCl	Sodium chloride
NOAEL	No-observed-adverse-effect-level
O&P	Ova and parasite (test)
OLE	Open-Label Extended Dosing (period)
PD	Pharmacodynamics
PE	Physical examination
PID	Patient identification number
PK	Pharmacokinetic(s)
PP	Per Protocol (population)
PPI	Proton pump inhibitor
PRO	Patient reported outcome
REML	Restricted maximum likelihood
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
CCI	[redacted]
Siglec	Sialic acid-binding, immunoglobulin-like lectin
SOC	System organ class
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse event of special interest
TNF	Tumor necrosis factor
TSS	Total symptom score
µL	Microliter
ULN	Upper limit of normal
WHODD	World Health Organization Drug Dictionary
w/v	Weight/volume

1. Protocol Synopsis

Study Title	A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AK002 in Adult and Adolescent Subjects with Active Eosinophilic Esophagitis
Sponsor	Allakos Inc., 975 Island Drive, Suite 201, Redwood City, CA 94065 USA
Number of Sites	Approximately up to 90 clinical centers globally
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 circulation. In the tissue, AK002 induces direct apoptosis of eosinophils and inhibition of mast cells.
Clinical Background	AK002, administered as a monthly intravenous infusion, has previously been tested in healthy volunteers and in subjects with indolent systemic mastocytosis (ISM), chronic urticaria, 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 subjects with ISM, chronic urticaria, severe AC, EG and/or EoD. In these studies, AK002 pharmaco-dynamic (PD) activity was observed for prolonged periods of time, and the AK002 pharmacokinetic (PK) parameters demonstrated a half-life amenable to administration every 4 weeks. To date, over 200 healthy volunteers and subjects with ISM, chronic urticaria, severe AC, mast cell gastritis, and EG and/or EoD have been enrolled in clinical studies. In general, AK002 has been well tolerated. The most common treatment-emergent adverse events (TEAE) observed were infusion-related reactions (IRR). Most IRR were mild to moderate; 2 IRR were classified as serious but resolved within 24 hours. Transient lymphopenia (a transient decrease in lymphocyte count) 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 and is consistent with the mechanism of action of AK002. In the randomized, double-blind, placebo-controlled, Phase 2 study of AK002 in 65 subjects with EG and/or EoD, subjects 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.

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 and duodenum at the high dose and low dose, respectively, versus a 10% increase for subjects on placebo ($p<0.0001$). The reduction of eosinophils was associated with a statistically significant reduction in total symptom score on 8 items (TSS8) of 58% in the high dose group, 49% in the low dose group versus 24% reduction in the placebo group ($p=0.0012$ and $p=0.015$, respectively). Improvement in symptoms was observed within 24 hours of the first dose of study drug. In addition, 70% of high dose treated subjects and 68% of low dose treated subjects were treatment responders (defined as >30% improvement in TSS and >75% reduction from baseline in tissue eosinophils) versus 5% for placebo-treated subjects ($p<0.0001$). Approximately 40% of subjects had concomitant eosinophilic esophagitis (EoE). In those subjects, a mean reduction of 95% of eosinophils/high powered field (hpf) was observed in the esophageal biopsies of AK002-treated subjects versus no change for placebo-treated subjects. Also, 13 of 14 (93%) subjects with EoE on AK002 were histologic responders (defined by ≤6 eosinophils/hpf) versus 1 of 11 (9%) subjects with EoE on placebo. Dysphagia improved by 53% in AK002-treated subjects versus 17% in placebo-treated subjects. AK002 was well tolerated with IRR being the only adverse event (AE) that occurred more frequently in AK002-treated subjects than placebo-treated subjects. More than 90% of subjects in the Phase 2 study elected to continue into a long-term continuation study (AK002-003X). In that study, a starting dose of 1 mg/kg was followed by doses of 3 mg/kg. Premedication of 80 mg oral prednisone was administered the day before the first and second doses in a substantial subset of subjects. No IRR were reported on the first or second infusions of AK002 when using this premedication regimen in the extension study (AK002-003X).
Target Disease Background and Rationale	Eosinophilic esophagitis represents the most common type of eosinophilic gastrointestinal disorders (EGID) and is characterized by chronic inflammation due to patchy or diffuse infiltration of eosinophils into layers of the esophagus (Collins, 2018; Dellon, 2018). Diagnosis is made based on clinical presentation combined with increased tissue eosinophils in biopsy specimens from the esophagus, without any other cause for the eosinophilia. Clinical manifestations of the disease include dysphagia, food impaction, refractory reflux, abdominal discomfort, nausea, and vomiting/regurgitation (Straumann, 2018). The symptoms are believed to be due to the release of inflammatory mediators from activated eosinophils, and possibly mast cells, resulting in inflammatory changes, including strictures (Abonia, 2010; Furuta, 2014). Active EoE has been defined by the presence of intramucosal eosinophilia with a peak count of ≥15 eosinophils/hpf (Dellon, 2018).

Target Disease Background and Rationale cont.	Chronic inflammation and progressive fibrosis in EoE lead to narrow caliber esophagus and formation of strictures. At the time of diagnosis, up to 67% of adults and 16% of children already have fibrostenotic disease (Warners, 2018). The pathogenesis of EoE is immune-mediated, triggered in response to food or environmental antigens. The initial Th2 inflammatory response with the release of various cytokines including IL-4, IL-5, IL-13, and Eotaxin-3 leads to trafficking of eosinophils to the esophageal mucosa, which is normally devoid of any eosinophils (Collins, 2018). The inflammatory infiltrate in EoE is most notable for the presence of eosinophils and mast cells, which appear to be the primary drivers of tissue damage and eventual development of fibrosis (Abonia, 2010; Collins, 2018). EoE is currently estimated to affect 4 out of every 10,000 persons in the United States (Dellon, 2014; Jensen, 2016). The incidence and prevalence of EoE is rapidly increasing, though whether this represents a true increase in incidence or is due to increased awareness and recent consensus on guidelines for diagnosis is unknown (Syed, 2012). Patients may also have concomitant atopic diseases like food allergy, asthma, and atopic dermatitis, which further impact patients' quality of life and contribute to health care costs. Also, 8% to 10% of patients with EoE may develop other eosinophilic gastrointestinal diseases like EG and/or EoD (Jensen, 2016). There are no FDA-approved treatments for EoE. Current therapies and disease management include dietary elimination, proton pump inhibitors (PPI), and topical or systemic steroids. Partial benefit has been observed with dietary elimination and PPI, but 40% to 50% of patients are refractory to these measures (Arias, 2014; Dellon, 2018; Dellon, Speck, 2014; Katz, 2013; Molina-Infante, 2016). In addition, responders to dietary elimination have demonstrated poor long-term adherence (Lucendo, 2013; Philpott, 2016; Reed, 2017). Corticosteroids, topical or systemic, have been shown to provide symptom relief but are not appropriate for long-term treatment due to numerous side effects and associated risks. Both topical (swallowed) and systemic corticosteroids have been shown to cause infection, adrenal insufficiency, bone demineralization, diminished growth, and cataracts (Furuta, 2015; Konikoff, 2006). Occasionally, in treatment-refractory cases, immunomodulatory biologics are attempted, but the role of biologics in treatment algorithms remains to be defined (Assa'ad, 2011; Clayton, 2014; Hirano, 2019; Hirano, 2017; Markowitz, 2018; Rothenberg, 2014; Spergel, 2012; Straumann, 2010). Given the chronic and progressive nature of the disease and lack of approved therapies, better treatment options are clearly needed to manage EoE. AK002 was tested in a randomized, double-blind, placebo-controlled, Phase 2 study in 65 subjects with EG and/or EoD. Subjects were randomized 1:1:1

Target Disease Background and Rationale cont.	to 1 of 3 dose groups: placebo, low dose regimen (4 monthly doses of AK002 at 0.3, 1, 1, and 1 mg/kg), or high dose regimen (4 monthly doses of AK002 at 0.3, 1, 3, and 3 mg/kg). All primary and secondary endpoints were met. There was a 97% and 92% mean reduction in eosinophils in the stomach and duodenum for the high dose group and low dose group, respectively, versus a 10% increase for placebo ($p<0.0001$). The reduction of eosinophils was associated with a statistically significant reduction in TSS8 of 58% in the high dose group, 49% in the low dose group, versus 24% reduction in the placebo group ($p=0.0012$). Approximately 40% of subjects with EG and/or EoD in the Phase 2 study had concomitant EoE. Of these subjects with concomitant EoE, those treated with AK002 had a 95% mean reduction in eosinophil count in esophageal biopsies versus no change in subjects treated with placebo. The reduction of eosinophils was associated with a 53% reduction in dysphagia on AK002 versus 17% on placebo. In addition, 13 of the 14 EoE subjects receiving AK002 were histological responders (defined as ≤6 eosinophils/hpf) at Week 14. 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 EoE. This Phase 2/3 study will evaluate the safety, tolerability, and clinical benefit of repeat doses of AK002 in adult and adolescent subjects with symptomatic EoE. Assessment of clinical benefit will include symptomatic, endoscopic, and histological improvement in disease.
Rationale for Dose Selection	Based on experience with AK002 in healthy volunteers and in subjects with ISM, chronic urticaria, severe AC, and EG and/or EoD, the proposed AK002 dose regimen of 6 total doses is 1 mg/kg for the first infusion, followed by either 1 mg/kg or 3 mg/kg administered every 4 weeks for 5 subsequent infusions. Subjects who complete randomized, double-blind, placebo-controlled treatment (all 6 doses of placebo or AK002) may have the option to receive 6 doses of open-label AK002 through participation in the Open-Label Extended Dosing (OLE) Period of the study. CCI [redacted]

Rationale for Dose Selection cont.	CCI  Twelve to 24 hours prior to the first dose of study drug, subjects will self-administer oral prednisone premedication (40 mg if body weight is <40 kg, 60 mg if body weight is ≥40 kg and <60 kg, or 80 mg if body weight is ≥60 kg). The proposed dose regimen in this EoE study is 6 doses of AK002 or placebo: 1 mg/kg for the first infusion, followed by either 1 mg/kg or 3 mg/kg administered every 4 weeks for 5 subsequent infusions (with the option to receive 6 additional infusions of open-label AK002 through the OLE period).
Number of Subjects	Approximately 300 subjects with symptomatic EoE will be randomized 1:1:1 to receive 1 of 3 dose regimens in a double-blind fashion: • 6 doses of placebo. • Low dose regimen: 1 mg/kg AK002 administered every 4 weeks for 6 doses. • High dose regimen: 1 mg/kg AK002 for the first dose followed by 3 mg/kg AK002 administered every 4 weeks for 5 subsequent doses. The power calculations for the number of subjects is described in Section 15.2, Sample Size. Subjects who successfully complete the randomized, double-blind, placebo-controlled treatment and the Day 169 visit may have the option to receive 6 doses of open-label AK002 through participation in the OLE period of the study.

Study Design	This is a Phase 2/3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and clinical benefit of AK002 in adult and adolescent subjects with active and biopsy-proven EoE. Subjects enrolled in the study will receive 6 infusions of placebo or AK002 administered every 4 weeks and will be followed for 8 weeks after the last dose. Subjects who successfully complete the randomized, double-blind, placebo-controlled treatment period of the study including the Day 169 visit may have the option to receive 6 doses of open-label AK002 through participation in the OLE period of the study. Subjects will be consented and then screened for 14 to 60 days (or a maximum of 35 days after the Screening EGD, whichever is shorter). During the screening period, a baseline, stable regimen of PPI and/or dietary intake will be established, if needed, and baseline disease activity data will be collected. Swallowed topical and systemic corticosteroids will not be allowed. Subjects who meet eligibility criteria can be enrolled into the study. Subjects 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. Subjects rescreened within 30 days of signing initial consent will not need to reconsent if there were no changes to the ICF. Prior to the first dose of study drug, subjects will be premedicated with oral prednisone (40 mg if body weight is <40 kg, 60 mg if body weight is ≥40 kg and <60 kg, or 80 mg if body weight is ≥60 kg). Subjects will self-administer oral prednisone 12–24 hours prior to the start of the first infusion only. Eligible subjects will receive the first dose of placebo or AK002 (1 mg/kg) on Day 1 and will remain confined to the clinic for at least 1 hour of observation (or greater, as per Investigator's discretion) following the end of the infusion. If the study drug is well tolerated (no stopping rules being met), subjects will continue to receive doses of placebo, 1 mg/kg AK002, or 3 mg/kg AK002 on Days 29, 57, 85, 113, and 141 for a total of 6 doses. Subjects will remain at the site for at least 1 hour of observation (or longer, as per the Investigator's discretion) after each dose. In the event of an IRR, the subject may require prolonged observation (>1 hour or until the symptoms resolve), as per the Investigator's discretion. Subjects will also be instructed to immediately contact the study doctor if any reactions occur after discharge. During the treatment period, subjects will return to the site for study visits as described in the Schedule of Events (Table 1). After completion of the Day 169 visit, the Investigator will evaluate whether the subject is eligible for the OLE period.

Study Design cont.	Only subjects who successfully complete the double-blind treatment period of the study including the Day 169 visit will have the option to receive 6 doses of open-label AK002 through participation in the OLE period, provided all eligibility criteria for the OLE period are satisfied. Subjects who are not eligible for (or who choose not to participate in) the OLE period will be followed for approximately 8 weeks after the last dose per the Schedule of Events (Table 1), including the Day 169 visit (4 weeks after the last dose) and the Day 197 visit (8 weeks after the last dose). Eligible subjects who choose to participate in the OLE period will begin following the OLE Schedule of Events (Table 5) and will receive the first dose of open-label AK002 approximately 1 week following Day 169. If absolute lymphocyte and/or eosinophil counts have not recovered (to normal range or baseline levels) by the Day 197 visit (or the Day 372 visit for subjects participating in the OLE period), extended follow-up visits are required approximately every 4 weeks to monitor blood counts until they recover. The study design is summarized as follows: • A 14 to 60-day screening period (or a maximum of 35 days after the Screening EGD, whichever is shorter) with evaluations for eligibility, including baseline disease activity (by daily Patient Reported Outcome [PRO] questionnaire) and Esophago-Gastro-Duodenoscopy (EGD) with biopsy. • Prior to the first dose of study drug, subjects will be premedicated with oral prednisone (40 mg if body weight is <40 kg, 60 mg if body weight is ≥40 kg and <60 kg, or 80 mg if body weight is ≥60 kg). Subjects will self-administer prednisone 12–24 hours prior to the first infusion only. • Eligible subjects will receive 6 doses of AK002 (or placebo) by IV infusion on Days 1, 29 (±3), 57 (±3), 85 (±3), 113 (±3), and 141 (±3). • A repeat EGD with biopsy will be performed on Day 169 (±3) or approximately 4 weeks after last dose if subject is terminated early. • After completion of the Day 169 visit, the Investigator will evaluate whether the subject is eligible for OLE. • Subjects who are eligible and choose to participate in the OLE period will begin following the OLE Schedule of Events (Table 5) on Day 176 (±3). The OLE period will include 6 doses of open-label AK002 administered on Days 176 (±3), 204 (±3), 232 (±3), 260 (±3), 288 (±3), and 316 (±3) and post-treatment follow-up visits on Day 344 (±7) and Day 372 (±7).

Study Design cont.	• Subjects who are not eligible for (or who choose not to participate in) the OLE period will be followed for approximately 8 weeks after the last dose per the Schedule of Events (Table 1), including the Day 169 visit (4 weeks after the last dose) and the Day 197 visit (8 weeks after the last dose). • If absolute lymphocyte and/or eosinophil counts have not recovered by Day 197 (or Day 372 for subjects in the OLE period), subjects will return approximately every 28 days for extended follow-up until counts recover. • Total study duration is approximately 33–36 weeks (or 58–61 weeks for subjects participating in the OLE period), though the study duration could be extended for monitoring absolute lymphocyte and/or eosinophil counts (as described above).
Primary Efficacy Objective	To evaluate the efficacy of AK002 in adult and adolescent subjects with active EoE when compared to placebo, efficacy endpoints will be co-primary: 1) The proportion of subjects who achieve a peak esophageal intraepithelial count of ≤6 eosinophils/hpf at Week24. 2) Mean change in Dysphagia Symptom Questionnaire (DSQ) score from Baseline to Weeks 23–24.
Secondary Objectives	To further evaluate the efficacy of AK002 in adult and adolescent subjects with active EoE when compared to placebo as measured by: 1) Percent change in peak esophageal intraepithelial eosinophil count at Week 24. 2) Proportion of subjects achieving peak esophageal intraepithelial eosinophil count of ≤1 eosinophil/hpf at Week 24. 3) Proportion of subjects achieving peak esophageal intraepithelial eosinophil count of <15 eosinophils/hpf at Week 24. 4) Proportion of treatment responders when a responder is a subject achieving >30% reduction in symptoms (DSQ) at Weeks 23–24 and achieving a peak intraepithelial eosinophil count of ≤6 eosinophils/hpf at Week 24. 5) Proportion of subjects with >50% reduction in DSQ score from Baseline to Weeks 23–24. 6) Percent change in DSQ score from Baseline to Weeks 23–24. 7) Change in biweekly mean DSQ over time. 8) Change in EoE Reference Score for Endoscopic Abnormalities from Baseline to Week 24.

Exploratory Objectives	To further evaluate the pharmacodynamic effect of AK002 in subjects with active EoE when compared to placebo as measured by: 1) Change in CCI [redacted] score from Baseline to Week 24. 2) Change in CCI [redacted] from Baseline to Week 24. 3) Change in CCI [redacted] from Baseline to Week 24.
Safety Objectives	To evaluate the safety and tolerability of AK002 in adult and adolescent subjects with active EoE by determining AE incidence and severity, study withdrawals due to AE, changes in vital signs and laboratory tests including immunogenicity, changes in concomitant medication beginning on or after the first infusion of study drug, and other safety parameters.
Subject Selection Criteria	**Inclusion Criteria** Subjects with active EoE are eligible to enroll in the study if all of the following criteria are met: 1) Male or female aged ≥12 and ≤80 years at the time of signing ICF. 2) Confirmed diagnosis of EoE and intraepithelial eosinophilic infiltration of ≥15 eosinophils/hpf in 1 hpf from a biopsy collected during the Screening EGD without any other cause for the esophageal eosinophilia. 3) Baseline DSQ (biweekly mean DSQ) score of ≥12 from the last 2 weeks of screening (the 14 days prior to the first dose) per the validated algorithm in Appendix 11. 4) History (by subject report) of an average of ≥2 episodes of dysphagia with intake of solid foods per week during the 4 weeks prior to screening. 5) Subjects must have failed or not be adequately controlled on standard of care treatments for EoE symptoms, which could include PPI, systemic or topical corticosteroids, and/or diet, among others. 6) If on an allowed treatment for EoE (per Section 8.2), stable dose for at least 4 weeks prior to screening and willingness to continue that dose for the study duration. 7) If subject is on preexisting dietary restrictions, willingness to maintain dietary restrictions throughout the study, as much as possible. 8) Able and willing to comply with all study procedures.

Subject Selection Criteria cont.	**Inclusion Criteria cont.** 9) Female subjects must be either post-menopausal for at least 1 year with FSH level >30 mIU/mL at screening or surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months, or if of childbearing potential, have a negative pregnancy test and either 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 the last dose of study drug, whichever is longer. Non-vasectomized male subjects 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 the last dose of study drug, whichever is longer. All fertile men with female partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect their partner might be pregnant at any time during study participation. **Exclusion Criteria** Subjects will be excluded if they meet any of the following criteria: 1) Concomitant moderately or severely symptomatic EG and/or EoD*, defined as: – ≥30 eosinophils/hpf in 5 hpf in the stomach (EG) and/or ≥30 eosinophils/hpf in 3 hpf in the duodenum (EoD) without any other cause for eosinophilia as determined by central histology assessment of biopsies collected during the Screening EGD ***and*** – EG/EoD PRO Questionnaire weekly average single symptom score of ≥3 during the last 2 weeks of screening for 1 of the following symptoms: abdominal pain, nausea, and/or diarrhea. * This exclusion criterion is only applicable to sites actively enrolling subjects in the AK002-016 study. If a site is ***not*** actively screening and enrolling subjects in the AK002-016 study, then this exclusion criterion is not applicable. 2) Causes of esophageal eosinophilia other than EoE or one the following: hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis, or peripheral blood absolute eosinophil count of >1500 eosinophils/μL. 3) History of inflammatory bowel disease, celiac disease, achalasia, and/or esophageal surgery.

Subject Selection Criteria cont.	**Exclusion Criteria cont.** 4) Any esophageal stricture unable to be passed with a standard diagnostic 9 mm to 10 mm upper endoscope or any critical esophageal stricture that requires dilation during screening. 5) History of bleeding disorders or esophageal varices. 6) History of malignancy; except carcinoma in situ, early stage prostate cancer, or non-melanoma skin cancers. However, cancers that have been in remission for more than 5 years and are considered cured, can be enrolled (with the exception of breast cancer). All history of malignancy (including diagnosis, dates, and compliance with cancer screening recommendations) must be documented and certified by the Investigator, along with the statement that in their clinical judgment the tissue eosinophilia is attributable to EGID, rather than recurrence of malignancy. 7) Active *Helicobacter pylori* infection (as determined by central histology staining of the biopsy collected during the Screening EGD), unless treated and confirmed to be negative prior to randomization and symptoms remain consistent. 8) Positive Ova and Parasite test at screening, seropositive for *Strongyloides stercoralis* at screening, and/or treatment for a clinically significant helminthic parasitic infection within 6 months of screening. 9) Seropositive for HIV or hepatitis at screening, except for vaccinated subjects or subjects with a history of hepatitis that has since resolved. 10) Prior exposure to AK002 or hypersensitivity to any constituent of AK002. 11) Change in dose of inhaled corticosteroids, nasal corticosteroids, PPI, and/or diet therapy within 4 weeks prior to screening. 12) Use of oral corticosteroids (swallowed topical or systemic corticosteroids) within 8 weeks prior to screening. 13) Use of any biologics or medications that may interfere with the study, such as immunosuppressive or immunomodulatory drugs including azathioprine, JAK inhibitors, 6-mercaptopurine, methotrexate, cyclosporine, tacrolimus, anti-TNF, anti-IL-4 receptor, e.g., dupilumab), anti-IL-5 (e.g., mepolizumab), anti-IL-5 receptor (e.g., benralizumab), anti-IL-13 (e.g., lebrikizumab), anti-IgE (e.g., omalizumab), within 12 weeks prior to screening. 14) Participation in a concurrent interventional study with the last intervention occurring within 30 days prior to administration of study drug or 90 days or 5 half-lives, whichever is longer, for biologic products.

Subject Selection Criteria cont.	**Exclusion Criteria cont.** 15) Vaccination with live attenuated vaccines ≤30 days prior to initiation of treatment in the study, during the treatment period, or vaccination expected ≤5 half-lives (≤4 months) following study drug administration (with the exception of a COVID-19 vaccine authorized by the FDA or other applicable regulatory agency). 16) Treatment with chemotherapy or radiotherapy in the preceding 6 months. 17) Presence of abnormal laboratory values considered by the Investigator to be clinically significant. 18) Any disease, condition (medical or surgical), or cardiac abnormality, which in the opinion of the Investigator, would place the subject at increased risk. 19) Known history of alcohol, drug, or other substance abuse or dependence. 20) Women who are pregnant, breastfeeding, or planning to become pregnant while participating in the study. 21) Any other reason that in the opinion of the Investigator or Medical Monitor makes the subject unsuitable for enrollment.
Test Product, Dose, and Administration	AK002 ([redacted]) and placebo are supplied as sterile liquids and will be diluted with 0.9% NaCl for IV injection. The injection will be administered through an infusion pump. AK002 and placebo are formulated in [redacted] pH 6.0, in Water for Injection. Prior to the first dose of study drug, subjects will be premedicated with oral prednisone (40 mg if body weight is <40 kg, 60 mg if body weight is ≥40 kg and <60 kg, or 80 mg if body weight is ≥60 kg). Subjects will self-administer oral prednisone 12–24 hours prior to the start of the first infusion only. AK002 at a dose of 1 mg/kg or placebo will be prepared according to the subject's body weight and administered over ≥4 hours on Day 1. Subsequent infusions of placebo or AK002 at a dose of 1 mg/kg or 3 mg/kg will be prepared on Day 29 (±3), Day 57 (±3), Day 85 (±3), Day 113 (±3), and Day 141 (±3). Depending on the subject's tolerance of the first and subsequent infusions (and at the Investigator's discretion), the second infusion can be given over ≥3 hours, and the subsequent 4 infusions can be given over ≥2 hours.
Duration of Subject Participation	The total study duration for each subject will be either 33–36 weeks or 58-61 weeks, including and depending on: • Screening period of 14–60 days (or a maximum of 35 days after the Screening EGD, whichever is shorter) prior to study drug administration.

Duration of Subject Participation cont.	• Treatment period of 24 weeks (±3 days) beginning the day of the first dose and ending 4 weeks after the last dose. • Optional Open-Label Extended Dosing Period of 28 weeks (±3 days), or Follow-up period of 4 weeks (±3 days). Regardless of whether a subject participates in the OLE period or not, all subjects will be followed for 8 weeks after the last dose of study drug. If lymphocyte or eosinophil counts have not recovered by Day 197 or Day 372 for subjects participating in the OLE period, subjects will return every 28 days for extended follow-up until counts have recovered.
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 Day 197 (±3 days) or Day 372 (for subjects participating in the OLE period) or Early Termination. Severity of AE will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (Version 5.0 or most current version). All AE will be assigned a severity grade and will be assessed for clinical significance and relationship to study drug. Additional safety evaluations include clinical laboratory tests, including anti-drug antibody to AK002, complete blood counts, chemistries, and urinalyses as well as physical exams and vital signs measurements. The Medical Monitor will review blinded safety data throughout the study. The safety monitor will review blinded safety data and escalate to the Medical Monitor as appropriate. An independent Data Monitoring Committee (iDMC) has been convened and will meet at regularly scheduled intervals in accordance with the iDMC charter. During the period of extended follow-up, data collection will be limited to hematology, serious adverse events, and adverse events of special interest.
Efficacy and Pharmacodynamic Evaluations	Biopsies of esophageal mucosa collected during pre-treatment and post-treatment EGD will be evaluated for number of eosinophils and per the CCI [redacted]. Additionally, the severity of endoscopic findings will be evaluated per the Eosinophilic Esophagitis Reference Score for Endoscopic Abnormalities (EREFS) during the EGD. The eosinophil counts in peripheral blood will be collected. Daily self-administration of a disease-specific patient questionnaire, the DSQ, will be used to evaluate signs and symptoms associated with EoE. If Question 1 of the DSQ is answered "No," the subject will receive the Solid Food Question (Appendix 2) after they complete and submit the DSQ. Subjects will rate CCI [redacted] CCI

Pharmacokinetic Evaluations	Blood (serum) will be collected for assessment of AK002 concentrations using a validated enzyme-linked immunosorbent assay method. Pharmacokinetic blood samples will be obtained on Days 1, 8, 15, 29, 57, 85, 113, 141, 169, and 197 (or ET). On dosing days (Days 1, 29, 57, 85, 113, and 141), blood for PK will be collected predose. Blood (serum) will be collected for assessment of AK002 anti-drug antibodies (ADA) using a validated assay method. ADA blood samples will be obtained predose on Days 1, 29, 57, 85, 113, 141, and 197 (or ET), and in the event of a suspected immunogenicity-related AE.
Sample Size Calculation	**First Co-Primary Endpoint:** A sample size of 8 subjects/treatment group will provide 90% power to demonstrate a statistically significant difference between any AK002 dose group and placebo in achieving histologic response (defined as the peak esophageal intraepithelial eosinophil count ≤6 cells/hpf) at Week 24. This calculation is based on the AK002-003 study in which 90% of AK002 subjects and 10% of placebo subjects achieved the histologic response at Day 99. The hypothesized treatment effect of 80% yielded a small number of subjects per group for the first co-primary endpoint. **Second Co-Primary Endpoint:** A sample size of 86 subjects/treatment group will provide 90% power to demonstrate a statistically significant difference between any AK002 dose group and placebo treatment group in mean absolute change in DSQ score from Baseline to Weeks 23–24. This calculation is based on the baseline score of 30 ± 15 (mean ± Standard Deviation [SD]) reported in the literature, and an expected mean reduction of 15 in any AK002 dose group and 7.5 in the placebo group, and a SD of 15 for the change from baseline (Dellon, 2017; Hirano, 2019; Hudgens, 2017). Consequently, approximately 100 subjects/treatment group will be included for a total of 300 subjects, driven by the second co-primary endpoint and potential 14% dropout rate.
Statistical Analysis	All subjects who received study medication will be included in the Safety Population for safety analysis. Subjects who are randomized and have received at least 1 dose of study medication will be included in the modified Intent-to-Treat (mITT) population for efficacy analysis. Subjects who meet mITT criteria and do not have significant protocol deviations interfering with efficacy assessment will be included in the Per Protocol (PP) population. The study statistician and study team will review protocol deviations to identify subjects to be excluded from the PP analysis population. The mITT population will be used for all efficacy analysis, and the PP population will be used for supplementary analyses of the primary endpoints and select secondary endpoints.

Statistical Analysis cont.	All subject data will be listed for the double-blind placebo-controlled portion of the study. 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 (CI) will be provided for the mean and proportion. No formal statistical inferences will be made for safety parameters. Safety data will be summarized for each treatment group as well as for the 2 active dose groups combined, unless otherwise specified. Baseline for all safety and efficacy endpoints is defined as the last observations before administration of the first IV infusion of study drug, unless otherwise specified. Subjects will be stratified at randomization based on age strata (12–17 and ≥18 years) and baseline DSQ score (≤30 and >30). Statistical analysis will be performed on completion of the double-blind, placebo-controlled portion of the study. On completion of the OLE period, additional statistical analyses will be performed on data collected in that period and for the entirety of the study. **Efficacy Analysis:** To evaluate the clinical benefit of AK002 in adult and adolescent subjects with active EoE when compared to placebo, efficacy endpoints will be co-primary. The first co-primary endpoint is the proportion of subjects who achieve a peak esophageal intraepithelial count of ≤6 eosinophils/hpf at Week 24. The endpoint will be analyzed using Fisher's exact test comparing the AK002 group and placebo group for the proportion of treatment responders. Subjects who experience an intercurrent event (ICE, e.g., exit the study prematurely or initiate prohibited medication or therapeutic EGD procedure) prior to the end of Week 24 will be treated as non-responders. The second co-primary endpoint is the mean absolute change in DSQ score from Baseline to Weeks 23–24. The DSQ score will be analyzed using ANCOVA with treatment as a factor, and Baseline DSQ and age strata as covariates. Baseline DSQ will be calculated using the DSQ scoring algorithm for all daily DSQ assessments collected during the 2 weeks prior to the first infusion of study drug. Data on subjects who experience an ICE (e.g., exit the study prematurely or initiate prohibited medications or therapeutic EGD procedure) prior to the end of Week 24 will be set to missing. Missing DSQ will be imputed using the Markov Chain Monte Carlo (MCMC) method.

Statistical Analysis cont.	Two sensitivity analyses will be conducted for the second co-primary endpoint. The first sensitivity analysis will be based on the placebo-based pattern-mixture model for the missing data imputation under the missing not at random (MNAR) assumption. In this model, subjects from the active treatment group after the ICE are assumed to behave like the subjects from the placebo group. Their missing data are imputed using the response profile from the placebo subjects who have similar baseline covariates and prior response trajectory. The second sensitivity analysis will utilize the tipping point method. In this method, the missing biweekly DSQ will be imputed with different adjustments for the active treatment subjects and placebo subjects under the MNAR assumption in search for a tipping point that reverses the study conclusion (i.e., p-value no longer <0.05 for the treatment effect). Change in continuous outcomes will be analyzed using a mixed model for repeated measures (MMRM) and will include fixed effects for age, baseline value, treatment, visit, and the treatment by visit interaction and allow for random subject effects. Treatment and visit will each be fitted as categorical variables. The model will assume unstructured covariance structure. If the model with unstructured covariance does not converge or it is determined to be inappropriate as outlined in the Guerin and Stroup study (Guerin, 2000), then other covariance structures will be considered to model the within-subject errors. The selection of the covariance structure for the final model will be handled in a hierarchical fashion, with the order being heterogeneous Toeplitz, AR(1), and compound symmetry, respectively. The Kenward-Rogers approach for computing denominator degrees of freedom will be used to account appropriately for pooling of within and between-subject variance estimates. The least squares means with 95% CI will be presented for each treatment*week cross-classification. A hierarchical procedure will be used to control the overall Type-I error rate at 0.05 for the primary endpoint and the secondary endpoints across the 2 AK002 dose regimens versus placebo. Each hypothesis will be formally tested only if the preceding hypothesis is significant at the 2-sided 0.05 significance level. The hierarchical testing order (all comparisons are with placebo) is detailed in the Statistical Analysis Plan. Percent change in peak esophageal intraepithelial eosinophil count at Week 24 will be analyzed by ANCOVA with age strata, baseline eosinophil count, and baseline DSQ as covariates. The proportion of subjects achieving peak esophageal intraepithelial eosinophil count of ≤1 eosinophils/hpf and <15 eosinophils/hpf at Week 24 will each be analyzed using Fisher's exact test.

Statistical Analysis cont.	The proportion of Treatment Responders, defined by subjects achieving >30% reduction in DSQ score (Weeks 23–24) and a peak esophageal intraepithelial eosinophil count of ≤6 eosinophils/hpf at Week 24, will be analyzed using Fisher's exact test. The proportion of subjects with >50% reduction in DSQ score from Baseline to Weeks 23–24 will be analyzed using the Cochran-Mantel-Haenszel test. The randomization stratum (age strata and baseline DSQ) will be used as the stratification factor for the analysis. Change in DSQ scores from Baseline to Weeks 23–24 will be analyzed similarly to that for the change in DSQ scores. The analysis of change in biweekly mean DSQ over time will employ the MMRM model similarly described above. Change in EoE Reference Score for Endoscopic abnormalities will employ the MMRM model similarly described above **Safety Analysis:** Subject incidence of treatment-emergent adverse events (TEAE) will be tabulated by MedDRA system organ class and preferred term and by severity and treatment relationship. Serious TEAE and TEAE leading to study discontinuation will be listed with pertinent information. Change from Baseline in laboratory tests will be summarized with descriptive statistics. Shift table will be presented. Vital signs will be summarized descriptively over time. Details of the analytical methods will be included in the Statistical Analysis Plan.

2. Background

2.1 Siglec-8 and AK002

Siglec-8, a member of the CD33-related family of sialic acid-binding, immunoglobulin-like lectins (Siglecs), is a transmembrane cell surface protein with restricted tissue distribution, expressed selectively on the surface of eosinophils, mast cells and, at lower levels, on basophils. 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 Siglec-8-positive target cells in vivo and in vitro.

2.2 Overview of Nonclinical Studies

AK002 is a humanized non-fucosylated immunoglobulin G1 (IgG1) monoclonal antibody directed against 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. 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 esophagitis (EoE).

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

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

2.3 Overview of Clinical Studies

AK002, administered as a monthly intravenous infusion, has previously been tested in healthy volunteers and in subjects with indolent systemic mastocytosis (ISM), chronic urticaria, severe allergic conjunctivitis (AC), mast cell gastritis, and eosinophilic gastritis (EG) and/or eosinophilic duodenitis (EoD), referred to as eosinophilic gastroenteritis (EGE) in previous studies.

Multiple doses of 3 mg/kg have been given to subjects with ISM, chronic urticaria, severe AC, mast cell gastritis, and EG and/or EoD. In these studies, AK002 pharmacodynamic (PD) activity was observed for prolonged periods of time and the AK002 pharmacokinetic (PK) parameters demonstrated a half-life amenable to administration every 4 weeks.

To date, 51 healthy volunteers (36 on AK002, 15 on placebo), 25 subjects with ISM, 47 subjects with chronic urticaria (including spontaneous and inducible), 30 subjects with severe AC, 8 subjects with mast cell gastritis, and 65 subjects with EG and/or EoD (43 on AK002 and 22 on placebo) have been enrolled in clinical studies.

In general, AK002 was well tolerated. The most common treatment-emergent adverse event (TEAE) observed was infusion-related reactions (IRR). Most IRR were mild to moderate and 2 IRR (1 in the healthy volunteer study and 1 in the AK002-003 study) were serious but resolved within 24 hours. Common symptoms of IRR were headache, nausea, sweating, flushing, and redness. Most IRR occurring during the infusion could be managed by slowing or temporary interruption of the infusion, with minimal intervention. In 6 healthy volunteers who received 2 doses of 0.3 mg/kg, 4 weeks apart, the second dose was better tolerated than the first dose. This is also the case in patients with ISM, chronic urticaria, severe AC, and EG and/or EoD; fewer adverse events (AE) were reported during the second and subsequent infusions when compared to the first infusion.

In all studies, a transient decrease in lymphocyte counts was observed after the AK002 infusion (usually resolving within 1 day) that was not associated with any clinical consequence, and a sustained depletion of eosinophils was observed that is 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 subjects with EG and/or EoD, subjects 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 mean reduction of 97% and 92% in eosinophils in the stomach and duodenum at the high dose and low dose AK002-treated subjects, respectively, versus a 10% increase for placebo-treated subjects ($p<0.0001$). The reduction of eosinophils was associated with a statistically significant reduction in total symptom score on 8 items (TSS8) of 58% in the high dose group, 49% in the low dose group versus 24% 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 AK002-treated subjects and 68% of low dose AK002-treated subjects were treatment responders (defined as >30% improvement in TSS and >75% reduction from baseline in tissue eosinophils) versus 5% of placebo-treated subjects ($p<0.0001$).

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

AK002 was well tolerated with IRR being the only AE that occurred more frequently in AK002-treated subjects than in placebo-treated subjects.

More than 90% of subjects in the Phase 2 study elected to continue into a long-term continuation study. In the long-term, open-label continuation 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 dose and second dose and, using this regimen, no IRR were reported for the first infusion of the continuation study.

2.4 Eosinophilic Gastrointestinal Disorders

Eosinophilic esophagitis represents the most common type of eosinophilic gastrointestinal disorders (EGID) and is characterized by chronic inflammation due to patchy or diffuse infiltration of eosinophils into layers of the esophagus (Collins, 2018; Dellon, 2014). Diagnosis is made based on clinical presentation combined with increased tissue eosinophils in biopsy specimens from the esophagus, without any other cause for the eosinophilia. Clinical manifestations of the disease include dysphagia, food impaction, refractory reflux, abdominal discomfort, nausea, and vomiting/regurgitation. The symptoms are believed to be due to the release of inflammatory mediators from activated eosinophils and possibly mast cells, resulting in inflammatory changes including strictures (Abonia, 2010; Furuta, 2014). Active EoE has been defined by the presence of intramucosal eosinophilia with a peak count of ≥15 eosinophils/hpf (Dellon, 2014).

Chronic inflammation and progressive fibrosis in EoE lead to narrow caliber esophagus and formation of strictures. At the time of diagnosis, up to 67% of adults and 16% of children already have fibrostenotic disease (Warners, 2018). The pathogenesis of EoE is immune-mediated, triggered in response to food or environmental antigens. The initial Th2 inflammatory response with the release of various cytokines including IL-4, IL-5, IL-13, and Eotaxin-3 leads to trafficking of eosinophils to the esophageal mucosa, which is normally devoid of any eosinophils (Collins, 2018). The inflammatory infiltrate in EoE is most notable for the presence of eosinophils and mast cells, which appear to be the primary drivers of tissue damage and eventual development of fibrosis (Abonia, 2010; Collins, 2018).

Eosinophilic esophagitis is currently estimated to affect 4 out of 10,000 persons in the United States (Dellon, 2014; Jensen, 2016). The incidence and prevalence of EoE is rapidly increasing, though whether this represents a true increase in incidence or is due to increased awareness and recent consensus on guidelines for diagnosis is unknown (Syed, 2012). Patients may also have concomitant atopic diseases like food allergy, asthma, and atopic dermatitis, which further impact patients' quality of life and contribute to health care costs. Also, 8%–10% of patients with EoE may develop other eosinophilic gastrointestinal diseases like EG and/or EoD (Jensen, 2016).

There are no FDA-approved treatments for EoE. Current therapies and disease management include dietary elimination, proton pump inhibitors (PPI), and topical or systemic steroids. Partial benefit has been observed with dietary elimination and PPI, but 40%–50% of patients are refractory to these measures (Arias, 2014; Dellon, 2014; Katz, 2013; Molina-Infante, 2016). In addition, responders to dietary elimination have demonstrated poor long-term adherence (Lucendo, 2013; Philpott, 2016; Reed, 2017). Corticosteroids, topical or systemic, have been shown to provide symptom relief but are not appropriate for long-term treatment due to numerous side effects and associated risks. Both topical (swallowed) and systemic corticosteroids have been shown to cause infection, adrenal insufficiency, bone demineralization, diminished growth, and cataracts (Furuta, 2015; Konikoff, 2006). Occasionally, in treatment-refractory cases, immunomodulatory biologics are attempted, but the role of biologics in treatment algorithms remains to be defined (Assa'ad, 2011; Clayton, 2014; Hirano, 2019; Hirano, 2017; Markowitz, 2018; Rothenberg, 2014; Spergel, 2012; Straumann, 2010). Given the chronic and progressive nature of the disease and lack of approved therapies, better treatment options are clearly needed to manage EoE.

AK002 was tested in a randomized, double-blind, placebo-controlled, Phase 2 study in 65 subjects with EG and/or EoD (previously referred to as EGE). Subjects were randomized 1:1:1 to 1 of 3 dose groups: placebo, low dose regimen (4 monthly doses of AK002 at 0.3, 1, 1, and 1 mg/kg), or high dose regimen (4 monthly doses of AK002 at 0.3, 1, 3, and 3 mg/kg). All primary and secondary endpoints were met. There was a 97% and 92% mean reduction in eosinophils in the stomach and duodenum at the high dose and low dose regimens, respectively, versus a 10% increase for placebo ($p<0.0001$). The reduction of eosinophils was associated with improvement in TSS of 58% in the high dose group, 49% in the low dose group, versus 24% reduction in the placebo-treated group ($p=0.0012$).

Approximately 40% of subjects with EG and/or EoD in the Phase 2 study had concomitant EoE, and these subjects had a 95% reduction in mean eosinophil count in esophageal biopsies associated with a substantial improvement in dysphagia on AK002 (53% reduction in dysphagia on AK002 versus 17% on placebo). In addition, 13 of the 14 EoE subjects receiving AK002 were histological responders with ≤6 eosinophils/hpf at Week 14.

By markedly reducing eosinophil numbers and inhibiting mast cell activity, AK002 may be useful in the treatment of patients with EoE. This Phase 2/3 study will evaluate the safety, tolerability, and clinical benefit of repeat doses of AK002 in adult and adolescent subjects with symptomatic EoE. Assessment of clinical benefit will include symptomatic, endoscopic, and histological improvement in the disease.

3. Rationale for Study and Dose Selection

Based on experience with AK002 in healthy volunteers and in subjects with ISM, chronic urticaria, severe AC, mast cell gastritis, and EG and/or EoD, the proposed AK002 dose regimen of 6 doses is 1 mg/kg for the first infusion, followed by either 1 mg/kg or 3 mg/kg administered every 4 weeks for 5 subsequent infusions.

Subjects who complete the double-blind, placebo-controlled treatment (all 6 doses of placebo or AK002) and the Day 169 visit may have the option to receive 6 doses of open-label AK002 through participation in the Open-Label Extended Dosing (OLE) Period of the study.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Twelve to 24 hours prior to the first infusion of study drug, subjects will self-administer oral prednisone premedication (40 mg if body weight is <40 kg, 60 mg if body weight is ≥40 kg and <60 kg, or 80 mg if body weight is ≥60 kg).

The proposed dose regimen in this EoE study is 6 doses of AK002 or placebo: 1 mg/kg for the first infusion, followed by either 1 mg/kg or 3 mg/kg administered every 4 weeks for 5 subsequent infusions (with the option to receive 6 additional infusions of open-label AK002 through participation in the OLE period).

4. Study Objectives

4.1 Primary Efficacy Objective

To evaluate the clinical benefit of AK002 in adult and adolescent subjects with active EoE when compared to placebo, efficacy endpoints will be co-primary:

1) The proportion of subjects who achieve a peak esophageal intraepithelial count of ≤6 eosinophils/hpf at Week 24.
2) Mean change in Dysphagia Symptom Questionnaire (DSQ) score from Baseline to Weeks 23–24.

4.2 Secondary Objectives

To further evaluate the clinical benefit of AK002 in adult and adolescent subjects with active EoE when compared to placebo as measured by:

1) Percent change in peak esophageal intraepithelial eosinophil count at Week 24.
2) Proportion of subjects achieving peak esophageal intraepithelial eosinophil count of ≤1 eosinophil/hpf at Week 24.
3) Proportion of subjects achieving peak esophageal intraepithelial eosinophil count of <15 eosinophils/hpf at Week 24.
4) Proportion of treatment responders when a responder is a subject achieving >30% reduction in symptoms (DSQ) at Weeks 23–24 and achieving a peak intraepithelial eosinophilic count of ≤6 eosinophils/hpf at Week 24.
5) Proportion of subjects with >50% reduction in DSQ score from Baseline to Weeks 23–24.
6) Percent change in DSQ score from Baseline to Weeks 23–24.
7) Change in biweekly mean DSQ over time.
8) Change in EoE Reference Score for Endoscopic Abnormalities (EREFS) from Baseline to Week 24.

4.3 Exploratory Objectives

The exploratory objectives are to further evaluate the effect of AK002 in adult and adolescent subjects with active EoE by comparing AK002 to placebo for the following parameters:

1) Change in CCI [redacted] from Baseline to Week 24.
2) Change in CCI [redacted] from Baseline to Week 24.
3) Change in CCI [redacted] from Baseline to Week 24.

4.4 Safety Objectives

To evaluate the safety and tolerability of AK002 in adult and adolescent subjects with active EoE by determining AE incidence and severity, study withdrawals due to AE, changes in vital signs and laboratory tests including immunogenicity, changes in concomitant medications beginning on or after the first infusion of study drug, and other safety parameters.

4.5 Target of Estimation

The estimand (target of estimation) for the study is:

> *In patients with active EoE, what is the between group (AK002 vs. Placebo) difference in the proportion of tissue eosinophil responders at Week 24, and between group difference in DSQ from baseline to Weeks 23–24 as measured by the patient-reported outcome (PRO) Dysphagia Symptom Questionnaire.*

The 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 clinical diagnosis of active EoE.

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 at Week 24 and change in DSQ 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 intercurrent events (ICE) confounding with the efficacy outcomes.

- Premature discontinuation from the study.
- Use of prohibited/restricted medication.
- Any therapeutic EGD (defined as dilatation or other intervention for a narrowing or stricture of the esophagus) at any point during the study through Week 24.

Intercurrent events are described above, and further clarification and handling of ICE including prohibited/restricted medications are detailed in the Statistical Analysis Plan (SAP).

4.5.5 Strategy for Handling Intercurrent Events

For analysis of the study product, the estimand tissue eosinophil values and DSQ scores 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?*

4.5.6 Summary Measure of the Estimand

- Percent (and 95% confidence interval [CI]) of subjects having tissue eosinophil response at Week 24 in the AK002 and placebo treatment groups and the absolute difference (and 95% CI) in the percent response between treatments.
- Least squares mean (LSM) (and standard error [SE]) of change from baseline to the DSQ of Weeks 23-24 and the between treatment difference in the AK002 and placebo treatment groups LSM.

5. Study Design

5.1 Study Overview

This is a Phase 2/3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and clinical benefit of AK002 in adult and adolescent subjects with active EoE. Subjects enrolled in the study will receive 6 infusions of placebo or AK002 administered every 4 weeks and will be followed for 8 weeks after the last dose.

Subjects who successfully complete the double-blind, placebo-controlled treatment period (including the Day 169 visit) may have the option to receive 6 doses of open-label AK002 through participation in the optional Open-Label Extended Dosing (OLE) Period of the study and will be followed for 8 weeks after the last dose.

Subjects will be consented and then screened for 14 to 60 days (or a maximum of 35 days after the Screening EGD, whichever is shorter). During the screening period, a baseline, stable regimen of PPI and/or dietary intake will be established, if needed, and baseline disease activity data will be collected. Swallowed topical corticosteroids and systemic corticosteroids will not be allowed. Subjects who meet eligibility criteria can be enrolled into the study. Subjects 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. Subjects rescreened within 30 days of signing the initial informed consent form (ICF) will not need to reconsent if no changes have been made to the ICF.

Prior to the first dose of study drug (12–24 hours prior to the infusion), subjects will be premedicated with oral prednisone (40 mg if body weight is <40 kg, 60 mg if body weight is ≥40 kg and <60 kg, or 80 mg if body weight is ≥60 kg). Subjects will self-administer oral prednisone 12–24 hours prior to the start of the first infusion only.

Eligible subjects will receive the first dose of placebo or AK002 (1 mg/kg) on Day 1 and will remain confined to the clinic for at least 1 hour of observation (or greater, as per Investigator discretion) following the end of the infusion. On Day 29, subjects will receive a second dose of placebo or AK002 (1 mg/kg or 3 mg/kg) and will remain confined to the clinic for at least 1 hour of observation (or greater, as per Investigator discretion) following the end of the infusion. If the study drug is well tolerated (no stopping rules met), subjects will continue to receive doses of placebo, 1 mg/kg AK002, or 3 mg/kg AK002 on Days 57, 85, 113, and 141 for a total of 6 doses. Subjects will remain at the site for at least 1 hour of observation (or longer, as per the Investigator's discretion) after each dose. In the event of an IRR, the subject may require prolonged observation (>1 hour or until the symptoms resolve), as per the Investigator's discretion. Subjects will also be instructed to immediately contact the study doctor if any reactions occur after discharge.

During the treatment period, subjects will return to the clinic for study visits as described in the Schedule of Events (Table 1). After completion of the Day 169 visit, the Investigator will evaluate whether the subject is eligible for the OLE period. Only subjects who successfully complete the double-blind treatment period (including the Day 169 visit) will have the option to participate in the OLE period, provided all eligibility criteria for the OLE period are satisfied.

Subjects who are not eligible for (or who choose not to participate in) the OLE period will complete the Follow-Up Period, including the Day 169 (±7) visit (4 weeks after the last dose) and the Day 197 (±7) visit (8 weeks after the last dose) per the Schedule of Events (Table 1).

Eligible subjects who choose to participate in the OLE period will begin following the OLE Schedule of Events (Table 5) and will receive the first dose of open-label AK002 approximately 1 week after Day 169 (on Day 176 ±3 days).

If absolute lymphocyte and/or eosinophil counts have not recovered (to normal range or baseline levels) by the Day 197 visit (or the Day 372 visit for subjects participating in the OLE period), extended follow-up visits are required approximately every 4 weeks to monitor blood counts until they recover.

The study design is summarized as follows:

- A 14 to 60-day (or a maximum of 35 days after the Screening EGD, whichever is shorter) screening period with baseline evaluations for eligibility, including baseline disease activity (by daily PRO questionnaire) and esophago-gastro-duodenoscopy (EGD) with biopsy.
- Prior to the first dose of study drug (12–24 hours prior to the infusion), subjects will be premedicated with oral prednisone (40 mg if body weight is <40 kg, 60 mg if body weight is ≥40 kg and <60 kg, or 80 mg if body weight is ≥60 kg).
- Eligible subjects will receive 6 doses of AK002 (or placebo) by IV infusion on Days 1, 29 (±3), 57 (±3), 85 (±3), 113 (±3), and 141 (±3). Subjects will self-administer prednisone 12–24 hours prior to the start of the first infusion only.
- Subjects will remain at the site for at least 1 hour of observation after each dose. In the event of an IRR, the subject may require prolonged observation (>1 hour or until the symptoms resolve), as per Investigator discretion. Subjects will also be instructed to immediately contact the study doctor if any reactions occur after discharge.
- A repeat EGD with biopsy will be performed on Day 169 (±3) or 28 (±3) days after last dose if subject is terminated early between Day 29 and Day 169 study visits.
- After completion of the Day 169 visit, the Investigator will evaluate whether the subject is eligible for the OLE period.
- Subjects who are eligible and choose to participate in the OLE period will begin following the OLE Schedule of Events (Table 5) on Day 176 (±3). The OLE period includes 6 doses of open-label AK002 administered on Days 176 (±3), 204 (±3), 232 (±3), 260 (±3), 288 (±3), and 316 (±3) and post-treatment follow-up visits on Day 344 (±7) and Day 372 (±7).

- Subjects who are not eligible for (or who choose not to participate in) the OLE period will be followed for approximately 8 weeks after the last dose per the Schedule of Events (Table 1). The Follow-Up Period includes the Day 169 (±7) visit (4 weeks after the last dose) and the Day 197 (±7) visit (8 weeks after the last dose).
- If absolute lymphocyte and/or eosinophil counts have not recovered by the Day 197 visit (or the Day 372 visit for subjects participating in the OLE period), subjects will return approximately every 28 days for extended follow-up until counts have recovered.
- Total study duration is approximately 33–36 weeks or 58–61 weeks for subjects participating in the OLE period, though the study duration could be extended for monitoring absolute lymphocyte and/or eosinophil counts (as described above).

5.2 Schedule of Events

The schedule of procedures and assessments (excluding the OLE period) is depicted in Table 1. The OLE schedule of procedures and assessments is depicted in Table 5 (Section 19.12.5).

Table 1 AK002-014 Schedule of Events

Description	Baseline/ Screening[2] (14–60 days)	Dose 1 Day 1[2]	Day 8 (±1 day)	Day 15 (±2 days)	Dose 2 Day 29 (±3 days)[35]	Dose 3 Day 57 (±3 days)[35]	Dose 4 Day 85 (±3 days)[35]	Dose 5 Day 113 (±3 days)[35]	Dose 6 Day 141 (±3 days)[35]	Day 169 (±3 days)[35] (or ET[32])	EOS Day 197 (±7 days)	Extended Follow-Up[33]
Informed consent	X											
Demographics and Medical History	X											
Stool for Ova and Parasite[3]	X											
ePRO Activation and Training[4]	X											
DSQ PRO[5]	*Daily from Screening through End of Study (or ET)* ---------->											
CCI	X			X	X							
EG/EoD PRO Questionnaire[7]	X											
CCI	X	X[1]			X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	
Baseline Diet Assessment[9]	X											
Baseline Diet Compliance[9]		X[1]		X	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	
Body Weight and Height[10]	X	X[1]			X[1]	X[1]	X[1]	X[1]	X[1]	X	X	
Vital Signs[11]	X	X[1]		X	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	
10 or 12-Lead ECG[12]	X											
Complete Physical Examination[13]	X											
EGD with Biopsy Collection[14]	X									X		
EREFS Scoring during EGD[15]	X									X		
Blood for Serology[16,17]	X											
Blood for Serum hCG and FSH[16,18]	X											
Blood for Total Serum IgE[16,19]		X[1]					X[1]			X		
Blood for CBC w/Differential[16,20]	X	X[1]	X	X	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X
Blood for Chemistry[16,21]	X	X[1]			X[1]	X[1]	X[1]	X[1]	X[1]	X	X	
Blood for PK[16,22]		X[1]	X	X	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	
Blood for ADA[16,23]		X[1]			X[1]	X[1]	X[1]	X[1]	X[1]		X	
Blood for Exploratory Analysis[16,24]	X			X						X	X	
Blood for Exploratory Safety[16,25]		X[1]			X[1]	X[1]	X[1]	X[1]	X[1]			

Table 1 AK002-014 Schedule of Events cont.

Description	Baseline/ Screening[2] (14-60 days)	Dose 1 Day 1[2]	Day 8 (±1 day)	Day 15 (±2 days)	Dose 2 Day 29 (±3 days)[35]	Dose 3 Day 57 (±3 days)[35]	Dose 4 Day 85 (±3 days)[35]	Dose 5 Day 113 (±3 days)[35]	Dose 6 Day 141 (±3 days)[35]	Day 169 (±3 days)[35] (or ET[32])	EOS Day 197 (±7 days)	Extended Follow-Up[33]
Urine for Urinalysis[16,26]	X	X[1]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	
Eligibility Assessment	X	X[1]										
Premedication – prednisone[28]	X[1]											
Urine Dipstick Pregnancy Test[16,27]		X[1]			X[1]	X[1]	X[1]	X[1]	X[1]			
Access IRT – IP Kit Assignment		X[1]			X[1]	X[1]	X[1]	X[1]	X[1]			
Study Drug Administration[29]		X			X	X	X	X	X			
Post-Dose Observation[29]		X			X	X	X	X	X			
Symptom-Directed Physical Exam[30]		X[1]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X[34]	X	
Adverse Events[31]	X	X	X	X	X	X	X	X	X	X	X	X
Open-Label Extended Dosing[34]										X[34]	X[34] – Day 197 visit does not apply to subjects in OLE period	

ADA: Anti-drug Antibody
CBC: Complete Blood Count
DSQ: Dysphagia Symptom Questionnaire
ET: Early Termination
ECG: Electrocardiogram
EGD: Esophago-gastro-duodenoscopy
FSH: Follicle-Stimulating Hormone
hCG: Human Chorionic Gonadotropin
IRT: Interactive Response Technology
IP: Investigational Product
PK: Pharmacokinetics

Table 1 Notes

1) Refer to assessment footnote for specific time points (e.g., predose, during infusion, postdose) to conduct the assessment on dosing days.

2) The screening period (Baseline) assessments can be conducted over multiple days within the screening period. The screening period must be a minimum of 14 days (2 weeks) and no longer than 60 days (or a maximum of 35 days after the Screening EGD, whichever is shorter). Day 1 can begin as soon as eligibility criteria are met.

3) Fecal collection kits for Ova and Parasite will be provided to subjects at the time of consent. Stool sample should be returned to the clinical site within 24 hours of collection.

4) At the time of consent, the Study Coordinator will activate all ePRO questionnaires in EDC, provide the subject with a unique username and password, train the subject on daily DSQ ePRO completion and compliance, and ensure the subject is able to complete the CCI questionnaire on their personal electronic device while on site.

5) Subjects should complete the DSQ daily after the last meal of the day. If Question 1 is answered "No," the subject should answer the Solid Food Question (Appendix 2) after the DSQ is completed and submitted. The site is responsible for monitoring compliance throughout the duration of the study and discussing compliance during study visits.

Table 1 Notes cont.

6) On Day -2 (2 days before Day 1), on Day 15 (approximately 2 weeks after the first dose), and on Day 29 (approximately 4 weeks after the first dose), subjects will self-administer the CCI after they submit the DSQ (and Solid Food Question, if applicable). On Day 15 and Day 29, subjects will also self-administer the CCI after the DSQ, Solid Food Question (if applicable), and CCI

7) During the screening period only, subjects should complete the EG/EoD PRO questionnaire daily after completion of the DSQ (and Solid Food Question, if applicable).

8) The CCI electronic questionnaire should be the first assessment completed by the subject at the beginning of the study visit prior to all other study visit assessments.

9) A baseline diet assessment will be performed using the standardized questions in Appendix 7. Eating patterns, food avoidance behaviors, and allergies will be captured. Per Inclusion Criteria #7, subjects should maintain baseline diet throughout the study. Diet compliance will be discussed during study visits, and any variance will be documented.

10) Height (in cm) and weight (in kg) will be measured at screening. Weight will also be measured predose on Days 1, 29, 57, 85, 113, 141, and on Days 169 and 197 (or ET).

11) Vital signs will be measured at baseline and on Days 1, 15, 29, 57, 85, 113, 141, 169, and 197 (or ET). On dosing days (Days 1, 29, 57, 85, 113, and 141), vital signs will be measured predose, 15 minutes (±5 minutes) after infusion start, immediately postdose (within 5 minutes after infusion end), and 1 hour (±5 minutes) postdose. Subject should be at rest for ≥5 minutes before vital signs (systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate) are measured.

12) Baseline ECG should be performed after the subject has been in the supine position for ≥5 minutes and, if done on the same day as blood collection, do before blood is drawn.

13) 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.

14) An EGD with biopsy collection will be performed during screening and at Day 169 (±3 days). EGD biopsies will be collected, processed, and shipped in accordance with Appendix 9, the lab manual, and the histology manual. Day 169 biopsy results will be blinded. If ET occurs after Day 29 and before Day 169, an EGD with biopsy collection should be done 28 (±3) days after the last dose (as part of the ET visit, see Table Note 32). If rescue therapy is required, an EGD (biopsy and EREFS) must be done prior to initiation of rescue medication or at the time of emergency dilation (instead of at Day 169).

15) During the Screening EGD and Day 169 EGD, severity will be evaluated using the EoE Reference Score for Endoscopic Abnormalities per the study histology manual.

16) Please see the study central laboratory manual for collection, processing, and shipment instructions. If possible, samples should be shipped on the same day as collection.

17) Blood for serology (Hepatitis B surface antigen, Hepatitis C antibody, Hepatitis B core antibody, and HIV) will be obtained during screening.

18) For female subjects, blood will be obtained during screening to test for hCG (pregnancy) and FSH (post-menopausal status).

19) Blood for total serum IgE will be obtained on Days 1 (predose), 85 (predose), and 169 or ET, if subject early terminates before Day 169.

20) Blood for CBC with differential will be obtained at all study visits. On Days 1, 29, 57, 85, 113, and 141, blood will be drawn twice (predose and 1-hour postdose). For every CBC with differential blood collection except screening and Day 1 (predose), the blood count results will be blinded to the Sponsor and the site. The safety monitor may request an unscheduled CBC with differential. Blood counts from Day 197 will be used to determine if extended follow-up is needed.

21) Blood for chemistry will be obtained during screening, predose on dosing days (Days 1, 29, 57, 85, 113, 141), and on Days 169 and 197 (or ET).

Table 1 Notes cont.

22) Blood for PK will be obtained on Days 1, 8, 15, 29, 57, 85, 113, 141, 169, and 197 (or ET). Blood will be drawn predose on Days 1, 29, 57, 85, 113, and 141.

23) Blood for ADA will be obtained predose on Days 1, 29, 57, 85, 113, and 141, on Day 197 (or ET), and in the event of a suspected immunogenicity-related AE.

24) Blood for exploratory analysis will be obtained during screening and on Days 15, 169, and 197 (or ET).

25) If an infusion-related reaction results in infusion interruption or cessation, blood for exploratory safety analyses will be obtained within 1–2 hours of symptom onset.

26) Urine for standard urinalysis will be obtained during screening, as needed (if warranted in the opinion of the Investigator or Subinvestigator), and on Day 197 (or ET).

27) For females of childbearing potential, urine for dipstick pregnancy test will be collected, tested, and results confirmed predose on Days 1, 29, 57, 85, 113, and 141.

28) The day before the first dose (12–24 hours prior to the planned infusion start time), eligible subjects will self-administer oral prednisone premedication based on body weight.

29) Study drug (or placebo) will be administered as a single peripheral IV infusion over ≥4 hours on Day 1, over ≥3 hours on Day 29, and over ≥2 hours for subsequent infusions (Days 57, 85, 113, and 141). Refer to the Pharmacy Manual for detailed instructions on preparation, administration, and infusion rate schedule requirements.

30) If a new or worsening symptom (or clinically significant finding) is observed or reported, the Investigator or designee will perform a symptom-directed physical examination. Symptom-directed physical examinations will be performed as needed and may be performed predose, during infusion, and/or postdose (including for possible IRRs).

31) All AE, including Adverse Events of Special Interest (AESI) and SAE, will be captured beginning from the start of the first infusion. Serious adverse events occurring between the time of consent and the start of the first study drug infusion will be reported only if they are assessed to be related to study procedures. For subjects participating in the OLE period, AE will be assessed and recorded in the CRF of the AK002-014 treatment period database up until the start of the first open-label infusion during the Day 176 visit and recorded in the CRF of the AK002-014 OLE period database beginning from the start of the first open-label infusion during the Day 176 visit.

32) ET visits should be conducted 28 (±3) days after the last dose of study drug or prior to this, if necessary, to ensure compliance with the visit. If a subject discontinues the study >28 days after the last dose of study drug, the ET visit should be conducted as soon as possible. If the subject is terminated after Day 29 and before Day 169, the ET visit will be performed 28 (±3) days after last dose and the ET visit will follow the Day 169 assessment schedule (including EGD with biopsy collection). If the subject is not participating in the OLE period and the ET visit occurs after Day 169, the Day 197 assessment schedule should be followed for the ET visit. See Table 5 OLE Period Schedule of Events for OLE period ET after Day 176.

33) If absolute lymphocyte and/or eosinophil counts do not recover (to normal range or baseline levels) by Day 197 (or ET), extended follow-up visits are required every 28 (±3) days) 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.

34) After completion of the Day 169 visit, the Investigator will evaluate whether the subject is eligible for the OLE period. If the subject is eligible, the subject will be given the option to participate in the OLE period beginning approximately 1 week after the Day 169 visit. Approximately 1 week after the Day 169 visit (on Day 176 ±3 days), eligible subjects that choose to participate in the OLE period will begin following the OLE Schedule of Events (Table 5) and will receive the first open-label AK002 infusion. For subjects participating in the OLE period, AE and concomitant medications should be collected and recorded in the AK002-014 Treatment Period database up until the start of the first open-label infusion during the Day 176 visit. This includes prednisone premedication administered prior to the Day 176 visit of the OLE period, which should be recorded in the Concomitant Medications CRF of both the AK002-014 treatment period database and the AK002-014 OLE period database.

35) Sites should strive to conduct visits within a ±3 day window, but visits conducted within ±7 days are acceptable and are not considered deviations. Visits conducted ±4-7 days from the target visit date should be minimized as much as possible. Any visit conducted outside of the ±3 day window should receive prior written approval from Allakos.

6. Criteria for Evaluation

6.1 Safety Endpoints

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

- Physical examination (Section 11.3.5, 11.3.6)
- Changes in vital signs (Section 11.3.4)
- Changes in Hematology (Section 11.2.8 and Section 11.4.1)
- Changes in Blood chemistry (Section 11.4.2)
- Changes in Urinalysis (Section 11.4.3)
- Anti-drug antibodies (Section 11.4.7)
- Treatment-emergent adverse events (Section 13) include severity, withdrawals due to AE, and other safety parameters.
- Changes in concomitant medications beginning on or after the first infusion of study drug (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 blood samples will be obtained on Days 1, 8, 15, 29, 57, 85, 113, 141, 169, and 197 (or ET). On dosing days (Days 1, 29, 57, 85, 113, and 141), blood for PK will be collected predose.

Blood (serum) will be collected for assessment of AK002 ADA using a validated assay method. ADA blood samples will be obtained predose on Days 1, 29, 57, 85, 113, and 141, on Day 197 (or ET), and in the event of a suspected immunogenicity-related AE.

6.3 Efficacy Endpoints

6.3.1 Co-Primary Efficacy Endpoints

1) The proportion of subjects who achieve a peak esophageal intraepithelial count of ≤6 eosinophils/hpf at Week 24.
2) Mean change in DSQ score from baseline to Weeks 23–24.

6.3.2 Secondary Efficacy Endpoints

To further evaluate the efficacy of AK002 in adult and adolescent subjects with active EoE when compared to placebo as measured by:

1) Percent change in peak esophageal intraepithelial eosinophil count at Week 24.
2) Proportion of subjects achieving peak esophageal intraepithelial eosinophil count of ≤1 eosinophil/hpf at Week 24.
3) Proportion of subjects achieving peak esophageal intraepithelial eosinophil count of <15 eosinophils/hpf at Week 24.
4) Proportion of treatment responders when a responder is a subject achieving >30% reduction in symptoms (DSQ) at Weeks 23–24 and achieving a peak intraepithelial eosinophilic count of ≤6 eosinophils/hpf at Week 24.
5) Proportion of subjects with >50% reduction in DSQ score from Baseline to Weeks 23–24.
6) Percent change in DSQ score from Baseline to Weeks 23–24.
7) Change in biweekly mean DSQ over time.
8) Change in EoE Reference Score for Endoscopic Abnormalities from Baseline to Week 24.

6.4 Exploratory Endpoints

1) Change in CCI [redacted] from Baseline to Week 24.
2) Change in CCI [redacted] from Baseline to Week 24.
3) Change in CCI [redacted] from Baseline to Week 24.

7. Subject Selection

7.1 Number of Subjects

Approximately 300 subjects with symptomatic EoE will be randomized 1:1:1 to receive 1 of 3 dose regimens in a double-blind fashion: placebo; the low dose regimen (1 mg/kg AK002 administered every 4 weeks for 6 doses); or the high dose regimen (1 mg/kg AK002 for the first dose followed by 3 mg/kg AK002 administered every 4 weeks for the 5 subsequent doses). Subjects who successfully complete the randomized, double-blind, placebo-controlled treatment period (including the Day 169 visit) may have the option to receive 6 doses of open-label AK002 through participation in the OLE period of the study.

7.2 Study Population

Male and female EoE subjects, aged ≥12 and ≤80 years who fulfill the eligibility criteria specified below.

7.3 Inclusion Criteria

Subjects with active EoE are eligible for enrollment into the study if all of the following criteria are met:

1) Male or female aged ≥12 and ≤80 years at the time of signing the ICF.

2) Confirmed diagnosis of EoE and intraepithelial eosinophilic infiltration of ≥15 eosinophils/hpf in 1 hpf from a biopsy collected during the Screening EGD without any other cause for the esophageal eosinophilia.

3) Baseline DSQ (biweekly mean DSQ) score of ≥12 from the last 2 weeks of screening (the 14 days prior to the first dose) per the validated algorithm in Appendix 11.

4) History (by subject report) of an average of ≥2 episodes of dysphagia with intake of solid foods per week during the 4 weeks prior to screening.

5) Subjects must have failed or not be adequately controlled on standard of care treatments for EoE symptoms, which could include PPI, systemic or topical corticosteroids, and/or diet, among others.

6) If on an allowed treatment for EoE (per Section 8.2), stable dose for at least 4 weeks prior to screening and willingness to continue that dose for the study duration.

7) If subject is on preexisting dietary restrictions, willingness to maintain dietary restrictions throughout the study, as much as possible.

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

9) Female subjects must be either post-menopausal for at least 1 year with FSH level >30 mIU/mL at screening or surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months, or if of childbearing potential, have a negative pregnancy test and either 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 the last dose of study drug, whichever is longer.

   Non-vasectomized male subjects 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 the last dose of study drug, whichever is longer. All fertile men with female partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect their partner might be pregnant at any time during study participation.

7.4 Exclusion Criteria

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

1) Concomitant moderately or severely symptomatic EG and/or EoD*, defined as:

   – ≥30 eosinophils/hpf in 5 hpf in the stomach (EG) and/or ≥30 eosinophils/hpf in 3 hpf in the duodenum (EoD) without any other cause for eosinophilia as determined by central histology assessment of biopsies collected during the Screening EGD.

   and

   – EG/EoD PRO Questionnaire weekly average single symptom score of ≥3 during the last 2 weeks of screening for 1 of the following symptoms: abdominal pain, nausea, and/or diarrhea.

   * This exclusion criterion is only applicable to sites actively enrolling subjects in the AK002-016 study. If a site is ***not*** actively screening and enrolling subjects in the AK002-016 study, then this exclusion criterion is not applicable.

2) Causes of esophageal eosinophilia other than EoE or one the following: hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis, or peripheral blood absolute eosinophil count >1500 eosinophils/µL.

3) History of inflammatory bowel disease, celiac disease, achalasia, and/or esophageal surgery.

4) Any esophageal stricture unable to be passed with a standard diagnostic 9 mm to 10 mm upper endoscope or any critical esophageal stricture that requires dilation during screening.

5) History of bleeding disorders or esophageal varices.

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

   All history of malignancy (including diagnosis, dates, and compliance with cancer screening recommendations) must be documented and certified by the Investigator, along with the statement that in their clinical judgment the tissue eosinophilia is attributable to EGID, rather than recurrence of malignancy.

7) Active *Helicobacter pylori* infection (as determined by central histology staining of the biopsy collected during the Screening EGD), unless treated and confirmed to be negative prior to randomization and symptoms remain consistent.

8) Positive Ova and Parasite test at screening, seropositive for *Strongyloides stercoralis* at screening, and/or treatment for a clinically significant helminthic parasitic infection within 6 months of screening.

9) Seropositive for HIV or hepatitis at screening, except for vaccinated subjects or subjects with a history of hepatitis that has since resolved.

10) Prior exposure to AK002 or hypersensitivity to any constituent of AK002.

11) Change in dose of inhaled corticosteroids, nasal corticosteroids, PPI, and/or diet therapy within 4 weeks prior to screening.

12) Use of oral corticosteroids (swallowed topical or systemic corticosteroids) within 8 weeks prior to screening.

13) Use of any biologics or medications that may interfere with the study, such as immunosuppressive or immunomodulatory drugs including azathioprine, JAK inhibitors, 6-mercaptopurine, methotrexate, cyclosporine, tacrolimus, anti-TNF, anti-IL-4 receptor (e.g., dupilumab), anti-IL-5 (e.g., mepolizumab), anti-IL-5 receptor (e.g., benralizumab), anti-IL-13 (e.g., lebrikizumab), and anti-IgE (e.g., omalizumab), within 12 weeks prior to screening.

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

15) Vaccination with live attenuated vaccines ≤30 days prior to initiation of treatment in the study, during the treatment period, or vaccination expected ≤5 half-lives (≤4 months) following study drug administration (with the exception of a COVID-19 vaccine authorized by the FDA or other applicable regulatory agency).

16) Treatment with chemotherapy or radiotherapy in the preceding 6 months.

17) Presence of abnormal laboratory values considered by the Investigator to be clinically significant.

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

19) Known history of alcohol, drug, or other substance abuse or dependence.

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

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

8. Prior and Concurrent Medications

Prior and concomitant medications (which include both prescribed and over-the-counter medications taken at any point beginning 30 days prior to the screening visit and until the end of study participation) will be recorded in the electronic Case Report Forms (eCRF). For subjects participating in the OLE period, concomitant medications should be recorded in the AK002-014 treatment period database up until the first open-label dose is administered during the Day 176 visit. This includes the prednisone premedication administered prior to the Day 176 visit in the OLE period, which should be recorded in the Concomitant Medications CRF of both the AK002-014 treatment period database and the AK002-014 OLE period database.

Subjects should be advised against taking any new medication or modifying the dose of existing medication, both prescribed and over the counter, without consulting the Investigator, unless the new medication or change in dose is required for emergency use. Immediately prior to the first infusion, study site personnel should ensure that the subject continues to meet the inclusion criteria and none of the exclusion criteria including no 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 also be documented.

8.1 Prohibited Medications

Any biologics or medications that may interfere with the study, such as swallowed corticosteroids, systemic corticosteroids, and systemic immunosuppressive or immunomodulatory drugs (including azathioprine, JAK inhibitors, 6-mercaptopurine, methotrexate, cyclosporine, tacrolimus, anti-TNF, anti-IL-4 receptor (e.g., dupilumab), anti-IL-5 (e.g., mepolizumab), anti-IL-5 receptor (e.g,. benralizumab), anti-IL-13 (e.g., lebrikizumab), anti-IgE (e.g., omalizumab), are prohibited for the duration of study participation.

The use of systemic or topical corticosteroids with a dose of >10 mg/day of prednisone or equivalent is prohibited unless it is due to unforeseen circumstances when it is deemed to be medically necessary to treat an unrelated medical condition or when given as a premedication prior to infusion or to treat an IRR that occurs during infusion. Any medications used for the treatment of IRR are not considered deviations from the protocol.

Subjects 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 medically necessary, rescue medications (systemic and/or swallowed topical corticosteroids) or emergency esophageal dilation may be used as rescue therapy. Any subject requiring rescue therapy must have an EGD (with biopsy collection and EREFS scoring) done prior to initiation

of rescue medications (or at the time of emergency esophageal dilation). The EGD performed due to initiation of rescue therapy will be used in place of the EGD scheduled for Day 169 (Week 24), and the subject will not have an EGD performed at the Day 169 (Week 24) visit. Subjects receiving rescue therapy should remain blinded, continue to receive study drug, and continue to comply with all study visits and assessments in accordance with the Schedule of Events (Table 1).

8.2 Allowed Medications

Medications, other than those that are prohibited (Section 8.1), such as antihistamines, leukotriene antagonists, sodium cromolyn, inhaled corticosteroids, nasal corticosteroids, PPI, and/or diet therapy are allowed during the study, and unless required due to unforeseen medical necessity, doses and/or dietary modifications are to remain stable. Systemic or swallowed corticosteroids with a dose of ≤10 mg/day of prednisone or equivalent are acceptable, as long as the dose remains stable throughout screening and during the study. All medication use will be documented in the eCRF.

Allakos allows all types and formulations of vaccines (including live attenuated vaccines) that are authorized by the FDA (or other applicable regulatory authority) for the prevention of COVID-19. These may be administered before, during, or after the study, but should not be administered within 7 days prior to or within 7 days after the administration of study drug (so the relationship of temporally-associated AE may be more easily assessed). Any vaccine for COVID-19 that is administered during the study collection period for concomitant medications will be recorded in the CRF. Additionally, any AE occurring during the study AE collection period will be recorded in the CRF.

There is no reason to believe there is any increased risk to a subject who receives both AK002 and a vaccine for the prevention of COVID-19. In addition, there is no reason to believe AK002 negatively impacts the efficacy of a vaccine for COVID-19. Allakos will continue to monitor subject safety on an ongoing basis, paying special attention to any subject who receives the vaccine.

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 IV 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.

Placebo is supplied as a sterile liquid in a single-use 10R glass vial with a fill volume of approximately 10.6 mL. Placebo contains CCI [redacted], pH 6.0, in sterile Water for Injection.

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

9.2 Study Drug Packaging and Labeling

AK002 drug product is supplied as a sterile liquid in a single-use 10R glass vial with a fill volume of approximately 10.6 mL. 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, kit number, Sponsor name, and directions for storage. Each vial will also contain a tear-off label with kit number and space to document subject ID and preparation date. This tear-off label should be applied to the Investigational Product (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 subject is entered into the Interactive Response Technology (IRT) system. Subsequent study drug shipments will be triggered automatically based on predetermined supply levels and enrollment activity at the site.

9.4 Study Drug Dosage/Dosage Regimen

Subjects will be randomly assigned through the IRT system to dosing groups of 1 mg/kg AK002 (6 doses at 1 mg/kg), 3 mg/kg AK002 (first dose at 1 mg/kg and 5 subsequent doses at 3 mg/kg), or placebo. Study drug vial labels will be blinded. The exact dose will be calculated prior to each infusion and based on subject's weight. Study drug will be administered as a single peripheral IV infusion using an infusion pump as indicated in the study Pharmacy Manual on Days 1, 29 (±3), 57 (±3), 85 (±3), 113 (±3), and 141 (±3). Eligible subjects that choose to participate in the OLE period will receive open-label AK002 administered at 1 mg/kg for the first OLE period infusion and either 1 mg/kg or 3 mg/kg for the subsequent OLE period infusions on Days 176 (±3), 204 (±3), 232 (±3), 260 (±3), 288 (±3), and 316 (±3).

9.5 Preparation of Study Drug

Study drug vial labels will be blinded and the study pharmacist (or designee) will prepare the study drug for each infusion. The designated study pharmacist will prepare the appropriate dilution of AK002 for IV administration based on the subject's weight obtained the day of dosing.

Appropriate aseptic technique will be used, and the drug will be prepared according to the Pharmacy Manual for AK002-014. Please refer to the Pharmacy Manual for additional details and step-by-step instructions regarding study drug preparation.

The infusion must be completed within 8 hours of preparation.

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 placebo or AK002 at a dose of 1 mg/kg will be prepared according to the subject's body weight and administered over ≥4 hours on Day 1. Subsequent infusions of placebo or AK002 at a dose of 1 mg/kg or 3 mg/kg will be prepared on Day 29 (±3), Day 57 (±3), Day 85 (±3), Day 113 (±3), and Day 141 (±3). Depending on the subject's tolerance of the first and subsequent infusions (and at the Investigator's discretion), the second infusion can be given over ≥3 hours, and the subsequent 4 infusions can be given over ≥2 hours. If the infusion is slowed or interrupted, the infusion length may exceed 4 hours but must be completed within 8 hours of preparation (prior to expiry). The same applies to the first and subsequent infusions in the OLE period of the study (for eligible subjects that choose to participate in the OLE period).

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

Prior to the first dose of study drug (12–24 hours prior to the infusion), subjects will be premedicated with oral prednisone (40 mg if body weight is <40 kg, 60 mg if body weight is ≥40 kg and <60 kg, or 80 mg if body weight is ≥60 kg). Subjects will self-administer oral prednisone 12–24 hours prior to the start of the first infusion only. As treatment assignment during the double-blind, placebo-controlled part of the study will be blinded, all eligible subjects that choose to participate in the OLE period of the study will self-administer oral prednisone premedication 12–24 hours prior to the first OLE period infusion as well.

The IV infusion may be interrupted, and/or the rate may be reduced if a subject 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 if a SAE occurs during the course of the infusion. If the subject experiences an IRR that causes interruption or cessation of the infusion, a blood sample for exploratory safety analysis should be collected within 1–2 hours of the onset of symptoms.

The subject will be observed for at least 1 hour (or greater, as per Investigator discretion) after the end of all infusions. In the event of an IRR, the subject may require prolonged observation (greater than 1 hour or until the symptoms resolve), as per Investigator discretion. At 1-hour postdose, vital signs will be measured and a blood sample will be collected for complete blood count (CBC) with differential. Subjects will also be instructed to immediately contact the study doctor if any reactions occur after discharge.

9.7 Study Drug Storage

AK002 will be stored by the study sites at 2°C to 8ºC under lock at the designated pharmacy. Access will be restricted to designated pharmacy staff. The NaCl 0.9% 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, this will be reported to the Sponsor or designee and captured as a deviation. The Sponsor will notify the site if the study drug is to be quarantined or can be used.

9.8 Study Drug Accountability

The site's study pharmacist/designee is responsible for maintaining accurate and current records accounting for receipt, dispensing, preparation, use, return (or destruction), and final disposition of all IP. All dosage calculations will be documented on the source documents. The Master IP Accountability Log and Endpoint IRT should be used to capture receipt, dispensing, and return (or destruction). The study monitor will verify entries on these documents throughout the study.

10. Subject Numbering, Stratification, Randomization, and Blinding

10.1 Subject Numbering

Each subject who provides informed consent will be assigned a patient identification number (PID) that uniquely identifies them as a subject 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 214.
- The second 3 digits designate the site number.
- The last 3 digits designate the order of consent at the site (the first subject who provides consent is 001, the second subject is 002, and so forth).

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

10.2 Stratification and Randomization

To be randomized into the study, a subject must meet all inclusion criteria and no exclusion criteria. Subjects will be randomized through the IRT system.

If the subject qualifies for the study after completing all screening procedures, on the day of first infusion (Study Day 1), the site will access the IRT system in order to randomize and stratify the subject in the study and enter the current body weight for study drug dose calculation. Subjects will be stratified at randomization based on age (12–17 and ≥18 years) and baseline DSQ score (≤30 and >30). The IRT system will randomly assign the subject to a low dose AK002 regimen (6 doses of 1 mg/kg), a high dose AK002 regimen (first dose at 1 mg/kg, subsequent 5 doses at 3 mg/kg), or placebo in a double-blind approach and will email the kit (vial) number to the study pharmacist.

Approximately 300 subjects with symptomatic EoE will be randomized 1:1:1 to receive 1 of 3 dose regimens in a double-blind fashion: 100 subjects will be randomized to the low dose regimen (1 mg/kg AK002 administered every 4 weeks for 6 doses); 100 subjects will be randomized to the high dose regimen (1 mg/kg AK002 for the first dose followed by 3 mg/kg AK002 administered every 4 weeks for the 5 subsequent doses); and 100 subjects will be randomized to placebo. A subject is considered enrolled in the study when the subject is randomized.

For subsequent infusions on Days 29, 57, 85, 113, and 141, the site will access the IRT system on the day of infusion and enter the PID as well as the subject's body weight, and the system will assign the vial(s) on the dose regimen associated with the randomization number. The study pharmacist will then receive an email detailing the kit (vial) number to prepare.

Prior to each infusion, the Investigator or designee will confirm that the PID recorded on the IV bag provided by the study pharmacist matches the subject. The subject's identification should be confirmed and documented by a second party prior to administering the infusion, whenever possible.

The assignment of treatments 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, subjects, or the primary 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 via the IRT system.
- Throughout the study, the blind should remain unbroken except for an emergency when knowledge of a subject'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.
- Study drug vial labels will be blinded, and AK002 and placebo for infusion will be identical in appearance.
- Results from analysis of blood samples for PK and ADA will not be provided to the Investigator and Sponsor until after final database lock.
- Results from analysis of blood samples for exploratory analysis or exploratory safety analysis (unless immediately required for safety issues) will not be provided to the Investigator and/or Sponsor until after final database lock of the double-blind portion of the study.
- For time points occurring after the initial infusion of study drug during the double-blind portion of the study, results of the following assessments will not be provided to the Investigator and/or Sponsor until after final database lock. 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) from peripheral blood.
  - Enumeration of eosinophils and CCI from Day 169 EGD biopsies.

Other than for the conditions described above, the study blind will be revealed after all subjects have completed their participation in the double-blind portion of the study and the database for the double-blind portion of the study has been locked.

10.4 Emergency Unblinding

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 subject was allocated would have implications for the emergency medical management of the subject or if required for regulatory reporting. If necessary, emergency unblinding can be conducted through the IRT system by registered site users and/or the Medical Monitor. Whenever possible, the Investigator should contact the Medical Monitor before performing an emergency breaking of the blind. Reason for unblinding, person conducting the unblinding, person(s) who know the unblinded treatment, and date/time of unblinding will be recorded.

Emergency unblinding is not appropriate if it becomes medically necessary to use rescue therapy (swallowed topical corticosteroids, systemic corticosteroids, or emergency esophageal dilation). Subjects receiving rescue therapy should remain blinded, should continue to receive study drug, and should continue to comply with all study visits and assessments in accordance with the Schedule of Events. Any subject requiring rescue therapy must have an EGD (with biopsy collection and EREFS scoring) performed prior to initiation of rescue medications or at the time of emergency dilation. The EGD performed due to the requirement of rescue therapy will be used instead of the EGD planned for Day 169 (Week 24).

11. Study Procedures and Guidelines

Table 1 provides the Schedule of Events depicting the required testing procedures to be performed for the duration of the study.

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

- During study visits:
  - CCI (self-administered electronic format) should be completed at the beginning of the study visit before any other assessments or procedures.
  - Vital signs will be obtained after the subject has been at rest for ≥5 minutes.
  - Physical examinations can be conducted and urine samples can be collected either before or after other evaluations, unless otherwise specified.

- Daily (after the last meal of the day):
  - DSQ (ePRO) should be completed daily after the last meal of the day (at approximately the same time each evening) during the screening, treatment, and follow-up periods.
  - Solid Food Question (if applicable) should be completed immediately after the DSQ.
  - On Day -2, Day 15, and Day 29, the CCI [redacted] should be completed immediately after the DSQ (and the Solid Food Question, if applicable) is submitted.
  - On Day 15 and Day 29, the CCI [redacted] should be completed immediately after the DSQ, Solid Food Question (if applicable), and the CCI [redacted] are submitted.
  - During the screening period only, subjects should complete the EG/EoD PRO questionnaire daily after completion of the DSQ, Solid Food Question (if applicable), and CCI [redacted] (on Day -2).

11.1 Dietary and Lifestyle Restrictions

Subjects should maintain the same diet and food restrictions from the screening visit through Day 197 (or ET). The Baseline Diet Assessment will capture the dietary and lifestyle restrictions adhered to prior to screening. Compliance with the baseline diet (previous dietary and lifestyle restrictions) will be captured in the eCRFs at subsequent study visits.

11.2 Pharmacodynamic/Efficacy-Related Procedures

11.2.1 Dysphagia Symptom Questionnaire

Throughout the duration of study participation (including screening period, treatment period, and follow-up period), subjects will self-administer an electronic version of the DSQ (Appendix 1) daily after the last meal of the day at approximately the same time each evening.

Subjects will not be able to complete a questionnaire more than 24 hours after it is due and will not be able to go back and make any corrections or changes to the data originally entered. This information will be automatically captured and maintained in the ePRO system of the EDC.

A paper version of the PRO questionnaire is available to subjects in case they are not able to complete the electronic version for a short period of time. Only one PRO 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.

11.2.2 Solid Food Question

If Question 1 on the DSQ is answered "No," the subject will receive the Solid Food Question (Appendix 2) after they complete and submit the DSQ. This information will be automatically captured and maintained in the ePRO system of the EDC.

A paper version of the Solid Food question is available to subjects in case they are not able to complete the electronic version for a short period of time. Only one PRO 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.

11.2.3 CCI [redacted]

On Day -2 (2 days before Day 1), on Day 15 (approximately 2 weeks after the first dose), and on Day 29 (approximately 4 weeks after the first dose), subjects will self-administer an electronic version of the CCI [redacted] (Appendix 3) after they complete and submit the DSQ and Solid Food Question (if applicable). This information will be automatically captured and maintained in the ePRO system of the EDC.

A paper version of the CCI [redacted] is available to subjects in case they are not able to complete the electronic version. This information will be manually captured and entered into the EDC by the study site.

11.2.4 CCI [redacted]

On Day 15 (approximately 2 weeks after the first dose) and Day 29 (approximately 4 weeks after the first dose), subjects will self-administer an electronic version of the CCI [redacted] (Appendix 4) after they complete and submit the DSQ, Solid Food Question (if applicable), and CCI [redacted] This information will be automatically captured and maintained in the ePRO system of the EDC.

A paper version of the CCI [redacted] is available to subjects in case they are not able to complete the electronic version for a short period of time. This information will be manually captured and entered into the EDC by the study site.

11.2.5 EG/EoD PRO Questionnaire

During the screening period only, subjects will self-administer an electronic version of the EG/EoD PRO questionnaire (Appendix 5) daily after completion of the daily DSQ, Solid Food Question (if applicable), and CCI [redacted] (on Day -2).

Subjects will not be able to complete a questionnaire more than 24 hours after it is due and will not be able to go back and make any corrections or changes to the data originally entered. This information will be automatically captured and maintained in the ePRO system of the EDC.

A paper version of the PRO questionnaire is available to subjects in case they are not able to complete the electronic version for a short period of time. Only one PRO 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.

11.2.6 CCI [redacted]

An electronic version of the CCI [redacted] (Appendix 6) will be self-administered by the subject via their personal electronic device during screening, predose on dosing days (Days 1, 29, 57, 85, 113, and 141), on Day 169, and on Day 197 (or ET). This information will be automatically captured and maintained in the ePRO system of the EDC.

A paper version of the CCI [redacted] is available to subjects in case they are not able to complete the electronic version at any given timepoint. This information will be manually captured and entered into the EDC by the study site.

11.2.7 Esophago-Gastro-Duodenoscopy

An EGD will be performed during the screening period and again on Day 169 (±3 days). During the EGD, endoscopic severity will be graded per the EoE Reference Score for Endoscopic Abnormalities and biopsies will be collected. Results from the Day 169 EGD biopsies will not be provided to the Investigator and/or Sponsor until after final database lock and unblinding. The Safety Monitor will review the EGD results and escalate any issues to the Medical Monitor and the Investigator, as appropriate, while maintaining the blind.

11.2.7.1 Eosinophilic Esophagitis Reference Score for Endoscopic Abnormalities

During the conduct of the EGD at screening and on Day 169 (or ET), the attending physician will assess and grade edema, rings, exudates, furrows, and strictures per the EREFS. The EREFS and the EREFS Scoring Tool source can be found in the study histology manual.

11.2.7.2 EGD Biopsy Collection

During the conduct of the EGD at screening and on Day 169 (or ET), a biopsy sample will be collected according to standardized instructions in the study histology manual and will be sent to the central histology lab for fixing and staining.

A blinded central reader will assess and report the maximum number of eosinophils/hpf, CCI [redacted]

CCI [redacted] CCI [redacted] (Appendix 9).

The Screening EGD biopsy tissue results must be available to verify eligibility per the following.

- Inclusion Criterion #2: Confirmed diagnosis of EoE and intraepithelial eosinophilic infiltration of ≥15 eosinophils/hpf in 1 hpf from the biopsy collected during the Screening EGD without any other cause for the esophageal eosinophilia.
- Exclusion Criterion #1: Concomitant moderately or severely symptomatic EG and/or EoD*, defined as:
  - ≥30 eosinophils/hpf in 5 hpf in the stomach (EG) and/or ≥30 eosinophils/hpf in 3 hpf in the duodenum (EoD) without any other cause for eosinophilia as determined by central histology assessment of biopsies collected during the Screening EGD.

  and

  - EG/EoD PRO Questionnaire weekly average single symptom score of ≥3 during the last 2 weeks of screening for 1 of the following symptoms: abdominal pain, nausea, and/or diarrhea.

  * This exclusion criterion is only applicable to sites actively enrolling subjects in the AK002-016 study. If a site is ***not*** actively screening and enrolling subjects in the AK002-016 study, then this exclusion criterion is not applicable.
- Exclusion Criterion #7: Active *Helicobacter pylori*** infection as determined by central histology staining of the biopsy collected during the Screening EGD.

  ** If an active *H. pylori* infection at screening is treated with standard of care therapies, the subject's symptoms remain stable, and the subject is then confirmed negative for *H. pylori*, the subject may be randomized into the study.

11.2.8 Complete Blood Count with Differential

Blood for CBC with differential will be obtained at all study visits. On dosing days (Days 1, 29, 57, 85, 113, and 141), blood for CBC with differential will be drawn twice: predose and 1 hour postdose.

The blood sample will be processed and shipped in accordance with the central laboratory manual and lab kit instructions. The 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).

As described in the Investigator's Brochure, expected effects of AK002 include changes in absolute lymphocyte and eosinophil counts, so these results could potentially unblind the blinded members of the study. Consequently, with the exception of screening and Day 1 predose, the CBC differential results (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) will be blinded to both the Sponsor and the study site. The CBC differential results for Day 1 (1 hour postdose), Days 8, 15, 29, 57, 85, 113, 141, 169, and 197 (or ET) will therefore be unavailable during the study and will not be provided to the Sponsor or study site until after final database lock and unblinding.

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.

If the CBC differential results from Day 197 (or ET) show that absolute lymphocyte and/or eosinophil counts have not recovered (to normal range or baseline levels), the subject must return for Extended Follow-Up visits approximately every 28 days to monitor blood counts until lymphocyte and/or eosinophil counts have recovered. Extended Follow-Up visits will consist only of blood collection for CBC with differential and collection of any AESI and SAE.

11.2.9 Baseline Diet Assessment

During the screening visit, the Investigator or designee will interview the subject and perform a Baseline Diet Assessment using the series of standardized dietary assessment questions found in Appendix 7. The Baseline Diet Assessment includes questions regarding eating patterns, food avoidance behaviors, and allergies, and will serve to establish the "Baseline Diet." Answers will be documented in the subject source documents and recorded in the eCRF.

If the subject is on diet therapy, the diet therapy and length of time on the current diet therapy will be documented during the Baseline Diet Assessment. Per Exclusion Criterion #11, the subject is ineligible if any changes were made to the diet therapy during the 8 weeks prior to screening. Additionally, if the Baseline Diet Assessment reveals preexisting dietary restrictions, the subject must be willing to maintain the same dietary restrictions ("Baseline Diet") for the entire duration of study participation per Inclusion Criterion #7.

11.2.10 Baseline Diet Compliance

Per Inclusion Criteria #7, the Baseline Diet (as defined and documented during the Baseline Diet Assessment) should be adhered to and maintained as much as possible for the entire duration of study participation, even if the subject feels the dietary restrictions are no longer necessary.

Compliance with the Baseline Diet will be discussed and assessed during study visits on Days 1, 15, 29, 57, 85, 113, 141, 169, and 197 (or ET). The Investigator or designee will document whether the subject was compliant with the Baseline Diet and, if not, all variances or deviations from the Baseline Diet will be documented in the source documents and eCRF.

11.3 Safety-Related Procedures

11.3.1 Concomitant Medications

All prior and concomitant medication and concurrent therapies will be documented at screening and assessed at all study visits. Concomitant medications, dose, route, unit, frequency of administration, indication for administration, dates of medication, and all changes will be captured. All prior medications (within 30 days before screening) and concomitant medications (during study participation from screening through Day 197 or ET) will be recorded.

For subjects participating in the OLE period, concomitant medications should be recorded in the AK002-014 treatment period database up until the first open-label dose is administered during the Day 176 visit. This includes the prednisone premedication administered prior to the Day 176 visit in the OLE period, which should be recorded in the Concomitant Medications CRF of both the AK002-014 treatment period database and the AK002-014 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 Stool Sample for Ova and Parasite

During the screening visit, subjects will be provided fecal collection kits for the Ova and Parasite (O&P) test. Subjects will take the kit home to collect a stool sample. Subjects must return the stool sample to the site on the day of collection (or within 24 hours of collection). The site will process and ship the stool sample per the central laboratory manual. The central laboratory will test the stool sample for O&P. Per Exclusion Criterion #8, a positive O&P result would make the subject ineligible, and a negative O&P result is required to confirm eligibility. Alternatively, a negative result from a helminth test done within 90 days prior to screening may be used to confirm eligibility, at the discretion of the Investigator.

11.3.3 Body Weight and Height

Height (in centimeters) and body weight (in kilograms) will be measured at screening and body mass index (BMI) will be calculated. Body weight must be measured prior to each dose of study drug (predose on Days 1, 29, 57, 85, 113, and 141). Predose weight should be measured at the site on the day before the study drug infusion or on the day of the study drug infusion, entered into the IRT system, and recorded on the IP Dose Calculation and Preparation Worksheet maintained by the study pharmacist for each subject's dose calculations.

Body weight will also be measured at the end of the treatment period (on Day 169) and at the end of study (Day 197 or ET).

11.3.4 Vital Signs

Vital signs including systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate will be taken after the subject has been at rest for ≥5 minutes and, if possible, before any blood draw.

Vital signs will be measured during screening and on Days 1, 15, 29, 57, 85, 113, 141, 169, and 197 (or ET). On dosing days (Days 1, 29, 57, 85, 113, and 141), vital signs will be measured predose, 15 minutes (±5 minutes) after the infusion start time, immediately postdose (within 5 minutes after the infusion end time), and 1 hour (±5 minutes) postdose. Please refer to the schedule in Table 1.

11.3.5 Complete Physical Examination

A complete physical exam will be performed during the screening visit by the Investigator or qualified Subinvestigator. A complete physical exam will 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.

The Investigator or qualified Subinvestigator will examine abnormalities and assess whether they are clinically significant or not clinically significant. All clinically significant abnormalities noted during the complete physical exam should be captured as a baseline condition in the Medical History source document and eCRF.

11.3.6 Symptom-Directed Physical Examination

If a new or worsening symptom (or clinically significant finding) is observed or reported, the Investigator (or qualified Subinvestigator) will perform a symptom-directed physical exam. The symptom-directed physical exam will focus only on body systems and/or organs with symptoms or warranting examination in the opinion of the Investigator or Subinvestigator. A symptom-directed physical exam will be performed only as needed, but may occur at any visit, predose, during infusions, and/or postdose (including for IRR). Clinically significant findings will be captured as an AE, followed by the Investigator, and managed appropriately per standard of care.

11.3.7 Electrocardiogram

A 10-lead or 12-lead ECG (without intensive QT analysis) will be obtained during screening after the subject has been in the supine position for ≥5 minutes and, if done on the same day as blood collection, before blood is drawn. The Investigator or qualified Subinvestigator will review

the ECG and assess any abnormalities for clinical significance. Any clinically significant findings will be captured as a baseline condition in the Medical History source document and eCRF. The ECG will be used to identify diseases or conditions that would put the subject at increased risk if participating in a clinical trial, so this should be considered when evaluating eligibility.

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 1. Investigators may have additional laboratory tests performed for the purpose of treatment planning or following AE or abnormal lab values. The site will process and ship blood and urine samples per central laboratory instructions. A central laboratory or designee will analyze blood and urine samples and provide results for the following clinical safety laboratory tests (Sections 11.4.1–11.4.10). 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 subject to be discontinued from the study, or
  - Requires a subject to receive treatment.

Clinical laboratory testing will be performed centrally but may be performed locally due to issues associated with the coronavirus pandemic.

Testing for COVID-19 is not required for this study but may be implemented by the study site at any time during the clinical study due to safety regulations or procedures.

11.4.1 Complete Blood Count with Differential

Blood will be obtained for CBC with differential as described in Section 11.2.8.

11.4.2 Blood Chemistry Profile

Blood will be obtained for chemistry tests during screening, predose on dosing days (Days 1, 29, 57, 85, 113, and 141), and on Days 169 and 197 (or ET). The blood sample will be processed and serum aliquots shipped per the central laboratory manual and laboratory kit instructions. The 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, alkaline phosphatase, alanine transaminase, aspartate transaminase, gamma-glutamyl transferase, and lactate dehydrogenase.

11.4.3 Urinalysis

Urine will be obtained for urinalysis during screening, as needed (if warranted in the opinion of the Investigator or Subinvestigator), and on Day 197 (or ET). The urine sample will be processed and shipped in accordance with the central laboratory manual and laboratory kit instructions. The central laboratory will analyze the urine sample for specific gravity, pH, protein, glucose, ketones, blood, and leukocyte esterase.

11.4.4 Serum Pregnancy and Follicle-Stimulating Hormone

Blood will be obtained from all female subjects of childbearing potential for a serum pregnancy test as measured by human chorionic gonadotropin (hCG). Females who are surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months and females who are postmenopausal for at least 1 year with FSH level >30 mIU/mL are not considered to be of childbearing potential. To determine whether female subjects are post-menopausal or are of childbearing potential, blood for serum FSH will be obtained from all females during screening. The blood sample will be processed and shipped per the central laboratory manual and laboratory kit instructions. Both serum hCG and serum FSH will be analyzed by the central laboratory.

Females of childbearing potential (females with screening FSH level ≤30 mIU/mL) will provide a urine sample predose on dosing days (Days 1, 29, 57, 85, 113, and 141) for pregnancy (hCG) testing. The site will perform the urine pregnancy (hCG) test using an indicator stick from the kit supplied by the central laboratory. This test is to be assessed by the study staff, and study staff should confirm the subject is not pregnant prior to the start of each study drug infusion.

11.4.5 Serology

Blood will be obtained during screening for serology tests including hepatitis B surface antigen (HbsAG), hepatitis C antibody, hepatitis B core antibody (anti-HBc), human immunodeficiency virus (HIV), and *Strongyloides stercoralis*. The blood sample will be processed and shipped to the central laboratory in accordance with the central laboratory manual and lab kit instructions.

Per Exclusion Criterion #8, subjects are not eligible if they are seropositive for *Strongyloides stercoralis*. Per Exclusion Criterion #9, subjects are not eligible if they are seropositive for HIV. Exclusion Criterion #9 also excludes subjects seropositive for hepatitis (HbsAG, hepatitis C antibody, or anti-HBc), except for vaccinated subjects or subjects with a history of hepatitis that has since resolved.

11.4.6 Total Serum IgE

Blood will be collected for total serum IgE on Day 1 (predose), Day 85 (predose), and Day 169 (or ET, if subject early terminates before Day 169). The blood sample will be processed and serum aliquots will be shipped frozen in accordance with the central laboratory manual and laboratory kit instructions. The central laboratory will analyze the serum samples for total serum IgE.

11.4.7 Anti-Drug (AK002) Antibodies

Blood for assessment of ADA will be collected predose on dosing days (Days 1, 29, 57, 85, 113, and 141) and at the end of study on Day 197 (or ET). In addition, an unscheduled blood sample for ADA may be obtained if an AE is suspected to be related to immunogenicity. The blood sample will be processed and serum aliquots shipped frozen in accordance with the central laboratory manual and lab kit instructions. The central laboratory will analyze the sample for ADA using a validated assay method.

11.4.8 Pharmacokinetics

Blood for assessment of AK002 concentrations (PK) will be collected on Days 1, 8, 15, 29, 57, 85, 113, 141, 169, and 197 (or ET). On dosing days (Days 1, 29, 57, 85, 113, and 141), blood for PK will be obtained predose. The blood samples will be processed and serum aliquots shipped frozen in accordance with the central laboratory manual and laboratory kit instructions.

AK002 concentrations will be assessed by the central laboratory (or designee) using a validated ELISA method. Refer to the central laboratory manual for additional information on PK sample collection, processing, storage, shipment, and analysis.

11.4.9 Blood for Exploratory Analysis

Blood samples for exploratory analyses will be collected during screening and on Days 15, 169, and 197 (or ET). The blood sample will be processed and serum aliquots shipped frozen in accordance with the central laboratory manual and laboratory kit instructions. Serum samples will be analyzed for exploratory biomarkers by the central laboratory or designee.

11.4.10 Blood for Exploratory Safety Analysis

There are no planned blood collections for exploratory safety. Blood will only be collected for exploratory safety if the infusion is interrupted or permanently discontinued due to an IRR. If an IRR results in infusion interruption or cessation, blood for exploratory safety should be obtained within 1–2 hours of IRR symptom onset. The blood sample will be processed and serum aliquots shipped frozen in accordance with the central laboratory manual and laboratory kit instructions. Exploratory safety analytes will be measured by the central laboratory or designee.

12. Evaluations and Procedures by Visit

Evaluations and procedures by visit are shown in Table 1.

General Information:

- All recorded clock times should utilize a 24-hour clock.
- Day 1 is the day of the first dose.
- Screening procedures may be performed over multiple days prior to the first dose.

12.1 Screening Period

1) Obtain written informed consent.
2) Begin the collection of SAE related to any screening activities.
3) Collect demographics and medical history.
4) Add the subject in EDC to assign a PID.
5) Complete in Screening Visit Date eCRF by selecting "Initiate Visit."
6) Activate electronic questionnaires (ePROs) and provide subject with ViedocMe username and PIN.
7) Train subject on daily completion of the DSQ, Solid Food Question (if applicable), and the EG/EoD PRO Questionnaire.
8) Have the subject complete the CCI questionnaire via ViedocMe using their personal electronic device while they are at the site. Remind the subject to begin completing the daily questionnaires after the last meal of the day.
9) Provide subject a stool collection kit and instruct them to return the stool sample to the site within 24 hours of collection (unless subject can provide sample while on site).
10) Perform Baseline Diet Assessment.
11) Record prior and concomitant medications.
12) Determine body weight and height.
13) Obtain vital signs before blood draws.
14) Perform a complete physical examination.
15) Obtain a 10-lead or 12-lead ECG before blood draw.

16) Collect the following samples for the central laboratory:
    a) Serum pregnancy test and FSH (for female subjects)
    b) Serology
    c) CBC with differential
    d) Chemistry
    e) Urinalysis
    f) Blood for exploratory analysis
17) Perform a Screening/Baseline EGD with endoscopic severity grading per EREFS and biopsy collection per the study histology manual.
18) Obtain Histology Results Report from the Central Histology Reader, confirm intraepithelial eosinophilic infiltration is enough to qualify the subject for the study and that there are no exclusionary criteria found on the EGD.
19) Evaluate eligibility on an ongoing basis as the screening assessment results are obtained.

12.2 The Day Before the First Infusion

1) Confirm eligibility.
2) Subject will self-administer oral prednisone premedication (dose based on body weight) 12–24 hours prior to the planned infusion start time. Ensure this is documented contemporaneously (e.g., subject emails the site when taking the premedication, subject texts the Study Coordinator when taking the premedication, etc.).

12.3 Day 1 – Dose 1

1) Pre-Infusion:
    a) Confirm continued eligibility.
    b) CCI to be self-administered by the subject via their personal electronic device.
    c) Document any changes to health status.
    d) Document any changes to concomitant medications including confirming and documenting the date and time the subject self-administered premedication.
    e) Document any changes to baseline diet.
    f) Determine body weight.
    g) Collect vital signs.

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

i) Collect the following samples for the central laboratory:

- Total Serum IgE
- CBC with differential
- Chemistry
- Pharmacokinetics
- Anti-drug antibodies
- Urinalysis, if warranted in the opinion of the Investigator or Subinvestigator

j) Perform urine pregnancy test (if subject is of childbearing potential).

k) Enter the subject's PID and body weight in the IRT system to randomize the subject.

l) Once the subject has been randomized in the IRT system, the pharmacist will receive an email with PID, body weight, and kit number.

m) The study pharmacist will prepare study drug using the weight obtained at the visit. The final combined volume of the IV bag of study drug + 0.9% NaCl will be **120** mL.

Note: **100 mL** of the calculated dose of study drug will be administered to the subject. The extra 20 mL is to be used to prime the IV infusion line during the preparation of the IV line at the bedside or to be left over in the infusion bag.

2) During the Infusion of Study Drug:

a) Infuse 100 mL of study drug over at least 4 hours using an infusion pump per the instructions and infusion rate schedule in the Administration of Investigational Product section of the Pharmacy Manual. 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) Perform symptom-directed physical exam, as needed.

d) If the subject experiences an IRR that causes an interruption or cessation of the study drug infusion, a blood sample should be collected within 1–2 hours of the onset of symptoms for exploratory safety analysis. An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

3) Post-Infusion:
    a) Subject will remain at the study site for at least 1 hour postdose for observation. In the event of an IRR, the subject may require prolonged observation (>1 hour or until the symptoms resolve), as per Investigator discretion.
    b) Perform symptom-directed physical exam, as needed.
    c) Collect vital signs immediately (+5 minutes) following the end of infusion and 1 hour (±5 minutes) postdose.
    d) Collect CBC with differential 1 hour (±15 minutes) after the end of the infusion.
    e) Subject will be instructed to immediately contact the study doctor if any reactions occur after discharge.

12.4 Day 8 (±1)

1) Document any changes to health status.
2) Document any changes to concomitant medications.
3) Collect the following samples for the central laboratory:
    a) CBC with differential
    b) Pharmacokinetics

12.5 Day 15 (±2)

1) Document any changes to health status.
2) Document any changes to concomitant medications.
3) Document any changes to baseline diet.
4) Collect vital signs.
5) Perform symptom-directed physical exam, as needed.
6) Collect the following samples for the central laboratory:
    a) CBC with differential
    b) Pharmacokinetics
    c) Blood for exploratory analysis
    d) Urinalysis, if warranted in the opinion of the Investigator or Subinvestigator

12.6 Day 29 (±3) – Dose 2

1) Pre-Infusion:

   a) Confirm continued eligibility.

   b) CCI to be self-administered by the subject via their personal electronic device.

   c) Document any changes to health status.

   d) Document any changes to concomitant medications.

   e) Document any changes to baseline diet.

   f) Determine body weight.

   g) Collect vital signs.

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

   i) Collect the following samples for the central laboratory:

      - CBC with differential
      - Chemistry
      - Pharmacokinetics
      - Anti-drug antibodies
      - Urinalysis, if warranted in the opinion of the Investigator or Subinvestigator

   j) Perform urine pregnancy test (if subject is of childbearing potential).

   k) Enter the subject's PID and body weight in the IRT system for IP kit assignment.

   l) The pharmacist will receive an email with PID, body weight, and kit number.

   m) The study pharmacist will prepare study drug using the weight obtained at the visit. The final combined volume of the IV bag of study drug + 0.9% NaCl will be **120** mL.

   Note: **100 mL** of the calculated dose of study drug will be administered to the subject. The extra 20 mL is to be used to prime the IV infusion line during the preparation of the IV line at the bedside or to be left over in the infusion bag.

2) During the Infusion of Study Drug:

   a) Infuse 100 mL of study drug over at least 3 hours using an infusion pump per the instructions and infusion rate schedule in the Administration of Investigational Product section of the Pharmacy Manual. 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) Perform symptom-directed physical exam, as needed.

d) If the subject experiences an IRR that causes an interruption or cessation of the study drug infusion, a blood sample should be collected within 1–2 hours of the onset of symptoms for exploratory safety analysis. An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

3) Post-Infusion:

a) Subject will remain at the study site for at least 1 hour postdose for observation. In the event of an IRR, the subject may require prolonged observation (>1 hour or until the symptoms resolve), as per Investigator discretion.

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

c) Collect vital signs immediately (+5 minutes) following the end of infusion and 1 hour (±5 minutes) postdose.

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

e) Subject will be instructed to immediately contact the study doctor if any reactions occur after discharge.

12.7 Day 57 (±3) – Dose 3

1) Pre-Infusion:

a) Confirm continued eligibility.

b) CCI to be self-administered by the subject via their personal electronic device.

c) Document any changes to health status.

d) Document any changes to concomitant medications.

e) Document any changes to baseline diet.

f) Determine body weight.

g) Collect vital signs.

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

i) Collect the following samples for the central laboratory:

- CBC with differential
- Chemistry
- Pharmacokinetics
- Anti-drug antibodies
- Urinalysis, if warranted in the opinion of the Investigator or Subinvestigator

j) Perform urine pregnancy test (if subject is of childbearing potential).

k) Enter the subject's PID and body weight in the IRT system for IP kit assignment.

l) The pharmacist will receive an email with PID, body weight, and kit number.

m) The study pharmacist will prepare study drug using the weight obtained at the visit. The final combined volume of the IV bag of study drug + 0.9% NaCl will be **120** mL.

Note: **100 mL** of the calculated dose of study drug will be administered to the subject. The extra 20 mL is to be used to prime the IV infusion line during the preparation of the IV line at the bedside or to be left over in the infusion bag.

2) During the Infusion of Study Drug:

a) Infuse 100 mL of study drug over at least 2 hours using an infusion pump per the instructions and infusion rate schedule in the Administration of Investigational Product section of the Pharmacy Manual. 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) Perform symptom-directed physical exam, as needed.

d) If the subject experiences an IRR that causes an interruption or cessation of the study drug infusion, a blood sample should be collected within 1–2 hours of the onset of symptoms for exploratory safety analysis. An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

3) Post-Infusion:

a) Subject will remain at the study site for at least 1 hour postdose for observation. In the event of an IRR, the subject may require prolonged observation (>1 hour or until the symptoms resolve), as per Investigator discretion.

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

c) Collect vital signs immediately (+5 minutes) following the end of infusion and 1 hour (±5 minutes) postdose.

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

e) Subject will be instructed to immediately contact the study doctor if any reactions occur after discharge.

12.8 Day 85 (±3) – Dose 4

1) Pre-Infusion:
   a) Confirm continued eligibility.
   b) CCI to be self-administered by the subject via their personal electronic device.
   c) Document any changes to health status.
   d) Document any changes to concomitant medications.
   e) Document any changes to baseline diet.
   f) Determine body weight.
   g) Collect vital signs.
   h) Perform symptom-directed physical exam, as needed.
   i) Collect the following samples for the central laboratory:
      - CBC with differential
      - Chemistry
      - Pharmacokinetics
      - Anti-drug antibodies
      - Total Serum IgE
      - Urinalysis, if warranted in the opinion of the Investigator or Subinvestigator
   j) Perform urine pregnancy test (if subject is of childbearing potential).
   k) Enter the subject's PID and body weight in the IRT system for IP kit assignment.
   l) The pharmacist will receive an email with PID, body weight, and kit number.
   m) The study pharmacist will prepare study drug using the weight obtained at the visit. The final combined volume of the IV bag of study drug + 0.9% NaCl will be **120** mL.

      Note: **100 mL** of the calculated dose of study drug will be administered to the subject. The extra 20 mL is to be used to prime the IV infusion line during preparation of the IV line at the bedside or to be left over in the infusion bag.

2) During the Infusion of Study Drug:
   a) Infuse 100 mL of study drug over at least 2 hours using an infusion pump per the instructions and infusion rate schedule in the Administration of Investigational Product section of the Pharmacy Manual. 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) Perform symptom-directed physical exam, as needed.

d) If the subject experiences an IRR that causes an interruption or cessation of the study drug infusion, a blood sample should be collected within 1–2 hours of the onset of symptoms for exploratory safety analysis. An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

3) Post-Infusion:

a) Subject will remain at the study site for at least 1 hour postdose for observation. In the event of an IRR, the subject may require prolonged observation (>1 hour or until the symptoms resolve), as per Investigator discretion.

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

c) Collect vital signs immediately (+5 minutes) following the end of infusion and 1 hour (±5 minutes) postdose.

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

e) Subject will be instructed to immediately contact the study doctor if any reactions occur after discharge.

12.9 Day 113 (±3) – Dose 5

1) Pre-Infusion:

a) Confirm continued eligibility.

b) CCI to be self-administered by the subject via their personal electronic device.

c) Document any changes to health status.

d) Document any changes to concomitant medications.

e) Document any changes to baseline diet.

f) Determine body weight.

g) Collect vital signs.

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

i) Collect the following samples for the central laboratory:

- CBC with differential
- Chemistry
- Pharmacokinetics
- Anti-drug antibodies
- Urinalysis, if warranted in the opinion of the Investigator or Subinvestigator

j) Perform urine pregnancy test (if subject is of childbearing potential).

k) Enter the subject's PID and body weight in the IRT system for IP kit assignment.

l) The pharmacist will receive an email with PID, body weight, and kit number.

m) The study pharmacist will prepare study drug using the weight obtained at the visit. The final combined volume of the IV bag of study drug + 0.9% NaCl will be **120** mL.

Note: **100 mL** of the calculated dose of study drug will be administered to the subject. The extra 20 mL is to be used to prime the IV infusion line during preparation of the IV line at the bedside or to be left over in the infusion bag.

2) During the Infusion of Study Drug:

a) Infuse 100 mL of study drug over at least 2 hours using an infusion pump per the instructions and infusion rate schedule in the Administration of Investigational Product section of the Pharmacy Manual. 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) Perform symptom-directed physical exam, as needed.

d) If the subject experiences an IRR that causes an interruption or cessation of the study drug infusion, a blood sample should be collected within 1–2 hours of the onset of symptoms for exploratory safety analysis. An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

3) Post-Infusion:

a) Subject will remain at the study site for at least 1 hour postdose for observation. In the event of an IRR, the subject may require prolonged observation (>1 hour or until the symptoms resolve), as per Investigator discretion.

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

c) Collect vital signs immediately (+5 minutes) following the end of infusion and 1 hour (±5 minutes) postdose.

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

e) Subject will be instructed to immediately contact the study doctor if any reactions occur after discharge.

12.10 Day 141 (±3) – Dose 6

1) Pre-Infusion:

   a) Confirm continued eligibility.

   b) CCI to be self-administered by the subject via their personal electronic device.

   c) Document any changes to health status.

   d) Document any changes to concomitant medications.

   e) Document any changes to baseline diet.

   f) Determine body weight.

   g) Collect vital signs.

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

   i) Collect the following samples for the central laboratory:

      - CBC with differential
      - Chemistry
      - Pharmacokinetics
      - Anti-drug antibodies
      - Urinalysis, if warranted in the opinion of the Investigator or Subinvestigator

   j) Perform urine pregnancy test (if subject is of childbearing potential).

   k) Enter the subject's PID and body weight in the IRT system for IP kit assignment.

   l) The pharmacist will receive an email with PID, body weight, and kit number.

   m) The study pharmacist will prepare study drug using the weight obtained at the visit. The final combined volume of the IV bag of study drug + 0.9% NaCl will be **120** mL.

      Note: **100 mL** of the calculated dose of study drug will be administered to the subject. The extra 20 mL is to be used to prime the IV infusion line during the preparation of the IV line at the bedside or to be left over in the infusion bag.

2) During the Infusion of Study Drug:

   a) Infuse 100 mL of study drug over at least 2 hours using an infusion pump per the instructions and infusion rate schedule in the Administration of Investigational Product section of the Pharmacy Manual. 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) Perform symptom-directed physical exam, as needed.

d) If the subject experiences an IRR that causes an interruption or cessation of the study drug infusion, a blood sample should be collected within 1–2 hours of the onset of symptoms for exploratory safety analysis. An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

3) Post-Infusion:

a) Subject will remain at the study site for at least 1 hour postdose for observation. In the event of an IRR, the subject may require prolonged observation (>1 hour or until the symptoms resolve), as per Investigator discretion.

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

c) Collect vital signs immediately (+5 minutes) following the end of infusion and 1 hour (±5 minutes) postdose.

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

e) Subject will be instructed to immediately contact the study doctor if any reactions occur after discharge.

12.11 Day 169 (±3) – Week 24

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

2) CCI to be self-administered by the subject via their personal electronic device.

3) Document any changes to health status.

4) Document any changes to concomitant medications.

5) Document any changes to Baseline Diet.

6) Determine body weight.

7) Obtain vital signs before blood draws.

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

9) Collect the following samples for the central laboratory:

a) CBC with differential

b) Chemistry

c) Pharmacokinetics

d) Total Serum IgE

e) Blood for exploratory analysis

10) Perform EGD

a) Assess and grade endoscopic severity per the EREFS using the EREFS Scoring Tool.

b) Biopsy collection per the AK002-014 Histology Manual, Central Laboratory Manual, and all EGD facility standard operating procedures (SOP).

11) Investigator to evaluate whether the subject is eligible for optional participation in the OLE period. Subjects who are eligible for and choose to participate in the OLE period will not follow the Evaluations and Procedures by Visit under Sections 12.12 and 12.13. Beginning on Day 176 (±3), eligible subjects who choose to participate in the OLE period will follow the OLE Schedule of Events (Table 5) in Appendix 12.

12.12 Day 197 (±7) – End of Study

1) CCI to be self-administered by the subject via their personal electronic device.

2) Document any changes to health status.

3) Document any changes to concomitant medications.

4) Document any changes to baseline diet.

5) Determine body weight.

6) Obtain vital signs before blood draws.

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

8) Collect the following samples for the central laboratory:

a) CBC with differential – blood counts determine if extended follow-up is required.

b) Chemistry

c) Pharmacokinetics

d) Anti-drug antibodies

e) Blood for exploratory analysis

f) Urinalysis

12.13 Early Termination

Perform 28 (±3) days after the last dose of study drug (or before, if necessary, to ensure compliance with the visit). If a subject discontinues the study more than 28 days after the last dose of study drug, the ET visit should be performed as soon as possible.

1) *If early termination occurs after Day 29 and prior to Day 169,* the subject should arrive fasting for the EGD procedure, as specified by instructions from the EGD provider.
2) CCI to be self-administered by the subject via their personal electronic device.
3) Document any changes to health status.
4) Document any changes to concomitant medications.
5) Document any changes to baseline diet.
6) Determine body weight.
7) Obtain vital signs before blood draws.
8) Perform symptom-directed physical exam, as needed.
9) Collect the following samples for the central laboratory:
    a) CBC with differential – blood counts determine if extended follow-up is required.
    b) Chemistry
    c) Pharmacokinetics
    d) Anti-drug antibodies
    e) Total Serum IgE *only if early termination occurs prior to Day 169*
    f) Blood for exploratory analysis
    g) Urinalysis
10) Perform EGD *only if early termination occurs after Day 29 and prior to Day 169*.
    a) Assess and grade endoscopic severity per the EREFS using the EREFS Scoring Tool.
    b) Biopsy collection per the AK002-014 Histology Manual, Central Laboratory Manual, and all EGD facility SOP.

12.14 Extended Follow-Up

Subjects must return to the site every 28 (±3) days to monitor absolute lymphocyte and eosinophil counts until recovery. Data collected during extended follow-up will be limited to:

1) CBC with differential
2) Adverse events of special interest
3) Serious adverse event

13. Adverse Event Reporting and Documentation

13.1 Adverse Events

In accordance with 21 Code of Federal Regulation (CFR) 312.32(b) and International Conference on Harmonisation (ICH) Guidance E2A, an adverse event is any untoward medical occurrence in a clinical investigation of a 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 an underlying medical condition.
- Significant abnormal findings from physical exams, vital signs, or laboratory tests.

The following examples are not considered an 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 a greater frequency than occurring at Baseline.

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 first administration of study drug and ending at the time of the Day 197 visit, the Day 372 visit (for subjects participating in the OLE period), or the ET visit, unless otherwise directed by Allakos. For subjects participating in the OLE period, AE will be assessed and recorded in the CRF of the AK002-014 treatment period database up until the start of the first open-label infusion during the Day 176 visit and recorded in the CRF of the

AK002-014 OLE period database beginning from the start of the first open-label infusion during the Day 176 visit.

13.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an AE that meets 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 an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed above.

SAE will be assessed and recorded after the first administration of study drug and ending at the time of the Day 197 visit, the Day 372 visit (for subjects participating in the OLE period), the ET visit, or the last Extended Follow-Up visit (if applicable), unless otherwise directed by Allakos. If an SAE that occurs during the screening period (after consent and before the first administration of study drug) is assessed to be related to a screening procedure, it will also be recorded.

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 especially active in protecting the body from parasitic infections and decreasing their function could theoretically increase the risk of parasitic and opportunistic infections.)
- Opportunistic infections (infections known to be more severe or occur more frequently in immunosuppressed populations) as confirmed by positive clinical laboratory test.
- Infusion-related reactions and hypersensitivity reactions including anaphylaxis.

Beginning from the time of first study drug infusion and ending at the time of the Day 197 visit, the Day 372 visit (for subjects participating in the OLE period), the ET visit, or the last extended follow-up visit (if applicable), any new AESI (or new information related to a previously reported AESI) must be recorded in the Adverse Event eCRF and designated as an "adverse event of special interest."

For subjects participating in the OLE period, AESI will be assessed and recorded in the CRF of the AK002-014 treatment period database up until the start of the first open-label infusion during the Day 176 visit and recorded in the CRF of the AK002-014 OLE period database beginning from the start of the first open-label infusion during the Day 176 visit.

13.4 Infusion-Related Reactions

All AE considered by the Investigator to be related to the infusion of the biological substance and occurring within 24 hours of the start of the study drug infusion should be captured as 1 IRR. Common symptoms of IRR include but are not exclusive 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 subject 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.

If the subject experiences an IRR that causes an interruption or cessation of the study drug infusion, a blood sample should be collected within 1–2 hours of the onset of symptoms for exploratory safety analysis.

Subjects will remain at the site for at least 1 hour of observation after each dose. If the subject experiences an IRR, prolonged observation (greater than 1 hour or until the symptoms resolve)

may be required, as per Investigator discretion. Subjects will also be instructed to immediately contact the study doctor if any reactions occur after discharge.

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

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

13.6 Evaluating Adverse Events and Serious Adverse Events

13.6.1 Establishing Diagnosis

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

13.6.2 Assessment of Intensity

The Investigator will use their clinical judgment as well as the guidelines laid out in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (Version 5.0 or most current version) (Table 2 and Appendix 8) to assess the intensity of each AE and SAE.

Table 2 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 adverse event.

* CTCAE version 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 adverse event is not necessarily a serious adverse event (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 3 to assess the relationship between study drug and AE.

Table 3 Adverse Event Relationship to Study Drug

Relationship to Study Drug	Comment
Related	There is clear evidence that the event is related to the use of study drug (e.g., confirmation by positive 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 4 to assess the relationship between study procedure and AE. Assessment of Causality to Study Procedure should include causality to such items as EGD with biopsy or blood draw (as appropriate), or other.

Table 4 Adverse Event Relationship to Study Procedure

Relationship to Study Procedure	Comment
Related	There is clear evidence that the event is related to a study procedure.
Possible	The event cannot be explained by the 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 early termination will be followed by the Investigator until event resolution, the AE is otherwise explained, not considered clinically significant by the Investigator, or the subject is lost to follow-up.

All AE identified, whether serious or non-serious, will be recorded in the Adverse Event eCRF beginning from the time of first study drug infusion and ending at the time of the Day 197 visit, the Day 372 visit (for subjects participating in the OLE period), or the ET visit, unless otherwise directed by Allakos. For subjects participating in the OLE period, AE will be assessed and recorded in the CRF of the AK002-014 treatment period database up until the start of the first open-label infusion during the Day 176 visit and recorded in the CRF of the AK002-014 OLE period database beginning from the start of the first open-label infusion during the Day 176 visit. Serious adverse events considered related to screening procedures will be recorded in the Adverse Event eCRF starting on the date of informed consent. Only AESI and SAE will be recorded in the Adverse Event eCRF during extended follow-up, if applicable. Whenever appropriate, the CTCAE (v. 5.0 or most current version) should be utilized for naming common AE (Appendix 8).

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.

Serious adverse event 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. The SAE must also be recorded on the Adverse Event eCRF and designated as “serious.”

Even when only minimal information is available for the initial SAE report, the Investigator should try to make a causality assessment, as the causality is used to determine the timing of regulatory reporting requirements. If the Investigator or designee is not available to sign the SAE report upon initial submission they should be contacted via telephone and their assessment documented on the SAE form (with a note stating signature is forthcoming). The Investigator **may change** the 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 subject source document. The site will notify the Institutional Review Board (IRB) according to its guidelines.

The subject'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 subject will be asked to return to the study site for further follow-up. If the condition is still ongoing at the time the subject exits the study, every effort will be made to continue to follow up with the subject 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 subject'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 (subject's or health care practitioner's refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Serious adverse events must be reported within 24 hours to:

SAE Reporting
Fax: +1-888-237-7475
Email: SAE@allakos.com

13.7.3 Pregnancy Reporting

Pregnancies are captured if they occur in female subjects or in the sexual partners of male subjects from the time the subject is first exposed to the investigational product through Day 141 (±3 days), Day 316 (for subjects participating in the OLE period), or ET.

Female subjects must be instructed to discontinue all study drugs and inform the Investigator immediately if they become pregnant during the study. Male subjects 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 subjects must be immediately discontinued from study drug. An uncomplicated pregnancy will not be considered an AE or SAE, but all pregnancies will be followed through term.

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

13.7.4 Adverse Events of Special Interest Reporting

Beginning from the time of first study drug infusion and ending at the time of the Day 197 visit, the Day 372 visit (for subjects participating in the OLE period), the ET Visit, or the end of the Extended Follow-Up period (if applicable), any new AESI (or new information related to a previously reported AESI) must be recorded in the Adverse Event eCRF and designated as an "adverse event of special interest."

For subjects participating in the OLE period, AESI will be assessed and recorded in the CRF of the AK002-014 treatment period database up until the start of the first open-label infusion during the Day 176 visit and recorded in the CRF of the AK002-014 OLE period database beginning from the start of the first open-label infusion during 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. AESI that are also SAE must be recorded in the Adverse Event eCRF and designated as both "serious" and an "adverse event of special interest." These will be reported on the Sponsor-provided SAE forms and should be reported to the Sponsor within 24 hours of site awareness.

13.8 Medical Monitoring

The Primary Medical Monitor or the Backup Medical Monitor should be contacted directly using the phone number and/or email address below to report medical concerns or for questions regarding safety.

Allakos AK002-014 Medical Monitors

PPD MD	PPD MD
Primary Medical Monitor	Backup Medical Monitor
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 throughout the study and will also convene as necessitated by data and/or safety reviews.

13.10 Study Withdrawal Criteria

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

- Occurrence of an exclusion criterion, which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor.
- Rebounding of eosinophil counts to >1500/μL in subjects 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 testing) without an alternative explanation.
- Elevation of ALT or AST >3 × ULN (confirmed by repeat testing) with the appearance or worsening of symptoms that the Investigator believes to be potentially related to hepatic inflammation such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or 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 an 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 trial in accordance with applicable regulations. The trial may be terminated or suspended on request of Health Authorities or Sponsor.

14. Discontinuation and Replacement of Subjects

14.1 Definition of Study Completion

A subject who does not participate in the OLE period and who completes visits through the Day 197 visit or, if applicable, the last Extended Follow-Up visit after completing Day 197, will be recorded as having completed the double-blind portion of the study.

A subject who completes visits through the Day 169 visit and participates in the OLE period of the study will be recorded as having completed the double-blind portion of the study.

A subject who participates in the OLE period of the study and completes visits through the Day 372 visit or, if applicable, the last Extended Follow-Up visit after completing Day 372, will be recorded as having completed the OLE portion of the study.

14.2 Early Discontinuation of Study Drug

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

- Subject withdraws consent.
- Adverse event that in the opinion of the Investigator results in study treatment discontinuation being in the best interest of the subject.
- Protocol violation requiring discontinuation of study treatment.
- Participation in any other study during the duration of this study.
- Use of a non-permitted concomitant drug without prior approval from the Medical Monitor.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration or treatment of either a psychiatric or physical (e.g., infectious disease) illness.

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

All subjects who discontinue study drug treatment should be encouraged to continue on study and complete assessments and procedures according to the follow-up period in Table 1, if possible (including follow-up EGD).

Reasonable attempts will be made by the Investigator to provide reasons for subject withdrawals. The reason for the subject's withdrawal from the study, or all attempts to acquire such, will be specified in the source documents.

Enrolled subjects who discontinue the study early will not be replaced.

15. Statistical Methods

15.1 General Considerations

This section outlines the nature and rationale for the statistical methods to be used for the analysis of the data from the study. A separate Statistical Analysis Plan (SAP), which will be documented as completed prior to unblinding the study, will describe data handling and statistical techniques in detail and will supersede the statistical methods described 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 observation before the first IV infusion of the study drug. All subject data will be listed for the double-blind placebo-controlled portion of the study. 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.

Unless otherwise specified, safety data will be summarized for each treatment group as well as for the 2 active dose groups combined.

Statistical analysis will be performed upon completion of the double-blind, placebo-controlled portion of the study. On completion of the OLE period, additional statistical analyses will be performed on data collected in that period and for the entirety of the study.

15.2 Sample Size

To achieve statistical significance for the first co-primary endpoint, a sample size of 8 subjects per treatment group will provide 90% power to demonstrate a statistically significant difference between any AK002 dose regimens and placebo in achieving histological response (defined as ≤6 eosinophils/hpf at Week 24). This calculation is based on the AK002-003 study in which 90% of AK002 subjects and 10% of placebo subjects achieved a histologic response at Day 99. The hypothesized treatment effect of 80% yielded a small number of subjects per group for the first co-primary endpoint.

To achieve statistical significance for the second co-primary endpoint, a sample size of 86 subjects per treatment group will provide 90% power to demonstrate a statistically significant difference between any AK002 dose group and placebo group in mean absolute change in DSQ score from Baseline to Weeks 23–24. This calculation is based on the baseline score of 30 ± 15 (mean ± SD) reported in the literature, and an expected mean reduction of 15 in the AK002 group and 7.5 in the placebo group, and a SD of 15 for the change from baseline (Dellon, 2017; Hirano, 2019; Hudgens, 2017).

Consequently, approximately 100 subjects per treatment group will be included for a total of 300 subjects, driven by the second co-primary endpoint and a potential dropout rate of 14%.

15.3 Data Sets Analyzed

All subjects who have received study medication will be included in the Safety population for safety analysis. Subjects who are randomized and have received at least 1 dose of study medication will be included in the Modified Intent-to-Treat (MITT) population for efficacy analysis. Subjects who meet MITT criteria and do not have significant protocol deviations interfering with efficacy assessment will be included in the Per Protocol (PP) population. The study statistician along with the study team will review protocol deviations to identify subjects to be excluded from the PP analysis population. The MITT population will be used for all efficacy analysis, and the PP population will be used for supplementary analyses of the primary endpoints and select secondary endpoints.

15.4 Subject Disposition

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

15.5 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

15.6 Study Drug Exposure

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

15.7 Efficacy Analysis

A hierarchical procedure will be used to control the overall Type I error rate at 0.05 for the primary endpoint and the secondary endpoints across the 2 AK002 dose regimens versus placebo. Each hypothesis will be formally tested only if the preceding hypothesis is significant at the 2-sided 0.05 significance level. The hierarchical testing order (all comparisons are with the placebo) is detailed in the SAP.

15.7.1 Primary Efficacy Endpoint Analysis

The first co-primary endpoint is the proportion of subjects who achieve a peak esophageal intraepithelial count of ≤6 eosinophils/hpf at Week 24. The endpoint will be analyzed using Fisher's exact test comparing the AK002 group and placebo group for the proportion of treatment responders. Subjects who experience an ICE (e.g., exit the study prematurely or initiate prohibited/rescue medication or therapeutic EGD procedure) prior to the end of Week 24 will be treated as non-responders.

The second co-primary endpoint is the mean change in DSQ score from Baseline to Weeks 23-24. The DSQ score will be analyzed using ANCOVA with treatment as a factor, and Baseline DSQ and age strata (12-17, ≥18) as covariates. The Baseline DSQ will be calculated using the DSQ scoring algorithm for all daily DSQ assessments collected during the 2 weeks prior to the first infusion of study drug.

Data on subjects who experience an ICE (e.g., exit the study prematurely or initiate prohibited/rescue medication or therapeutic EGD procedure) prior to the end of Week 24 will be set to missing. Missing DSQ will be imputed using the Markov Chain Monte Carlo (MCMC) method.

Two sensitivity analyses will be conducted for the second co-primary endpoint. The first sensitivity analysis will be based on the placebo-based pattern-mixture model for the missing data imputation under the missing not at random (MNAR) assumption. In this model, subjects from the active treatment group after the ICE are assumed to behave like the subjects from the placebo group. Their missing data are imputed using the response profile from the placebo subjects who have similar baseline covariates and prior response trajectory. The second sensitivity analysis will utilize the tipping point method. In this method, the missing biweekly DSQ will be imputed with different adjustments for the active treatment subjects and placebo subjects under the MNAR assumption in search for a tipping point that reverses the study conclusion (i.e., p-value no longer <0.05 for the treatment effect).

Change in continuous outcomes will be analyzed using a mixed model for repeated measures (MMRM) and will include fixed effects for baseline value, treatment, week. and the treatment-by-week interaction and allow for random subject effects. Treatment and week will each be fitted as categorical variables. Model will assume unstructured covariance structure. If the model with unstructured covariance does not converge or it is determined to be inappropriate as outlined in the Guerin and Stroup study, (Guerin, 2000), then other covariance structures will be considered to model the within-subject errors. The selection of the covariance structure for the final model will be handled in a hierarchical fashion with the order being heterogeneous Toeplitz, AR(1), and compound symmetry, respectively. The Kenward-Rogers approach for computing denominator degrees of freedom will be used to account appropriately for pooling of within and between-subject variance estimates. The LSM with 95% CI will be presented for each treatment*week cross-classification.

15.7.2 Secondary Efficacy Endpoint Analysis

The percent change in peak esophageal intraepithelial eosinophil count at Week 24 will be analyzed using ANCOVA with treatment as a factor and baseline eosinophil counts, baseline DSQ, and age strata as covariates. The LSM, SE, and 95% CI for individual treatment groups, and the LSM, SE, 95% CI, and p-value for the between treatment difference will be presented.

Proportion of subjects achieving peak esophageal intraepithelial eosinophil count of ≤1 eosinophil/hpf at Week 24 will be analyzed using Fisher's exact test.

Proportion of subjects achieving peak esophageal intraepithelial eosinophil count of <15 eosinophil/hpf at Week 24 will be analyzed using Fisher's exact test.

Proportion of Treatment Responders, defined by subjects with ≥30% improvement in DSQ score at Weeks 23–24 and a peak esophageal intraepithelial eosinophil count of ≤6 eosinophils/hpf at Week 24, will be analyzed using Fisher's exact test.

Proportion of subjects with >50% reduction in DSQ score from Baseline to Weeks 23–24 will be analyzed using the Cochran-Mantel-Haenszel (CMH) test. The randomization stratum (age and baseline DSQ) will be used as the stratification factor for the analysis.

Change in DSQ scores from Baseline to Weeks 23–24 will be analyzed using MMRM and will include fixed effects for age, baseline DSQ, treatment, visit, treatment-by-visit interaction, and allow for random subject effects.

The analysis of change in biweekly mean DSQ over time will employ MMRM similarly as described above.

Change in EoE Reference Score for Endoscopic Abnormalities from Baseline will be summarized and analyzed using MMRM with age, treatment, visit, and treatment-by-visit interaction as fixed factors and baseline peripheral blood eosinophil count and baseline DSQ (continuous) as covariates.

15.7.3 Exploratory Endpoint Analysis

Change in continuous exploratory endpoints will be analyzed using MMRM and will include fixed effects for age, baseline value, treatment, visit, and treatment-by-visit interaction and allow for random subject effects. Treatment and visits will be fitted as categorical variables.

15.8 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 IV infusion of the study medication.

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

- Overview of TEAE will include:
  - Number (%) of subjects who reported at least 1 TEAE overall, by maximum severity, and by strongest relationship
  - Number (%) of subjects who reported at least 1 serious TEAE
  - Number (%) of subjects who reported at least 1 TEAE leading to treatment discontinuation
  - Number (%) of subjects who reported at least 1 TEAE leading to study discontinuation
  - Number (%) of subjects who reported at least 1 TEAE of special interest (TEAESI)
- TEAE by preferred term in descending order of subject incidence
- TEAE by SOC and preferred term
- TEAE by maximum severity, SOC, and preferred term
- Drug-related TEAE by SOC and preferred term
- TEAE leading to treatment discontinuation by SOC and preferred term
- Serious TEAE by SOC and preferred term
- TEAESI by SOC and preferred term

Clinical Laboratory Assessments: Descriptive statistics will be used to summarize hematology, chemistry, and urinalysis 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. Number (and %) of subject incidence of positive ADA tests will be summarized.

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

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

Physical Exam: New or worsening symptoms in the symptom-directed physical exams will be included in the by-subject data listing.

Prior and Concomitant Medications: All medications (prior and concomitant) will be coded using the most current World Health Organization Drug Dictionary (WHODD). Prior and concomitant medications will be summarized with subject and percent incidence by Anatomical Therapeutic Chemical Class and preferred term.

15.9 Subject Confidentiality

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

Only the PID, subject initials, and demographics will be recorded in the eCRF to the extent allowed by country requirements. If the subject 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 subject identifying information.

All study findings will be stored in electronic databases. The subjects 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. Subjects will be informed that all personal information made available for inspection will be kept confidential to the extent permitted by all applicable state, local, and federal data protection/privacy laws and/or regulations and will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential. At study check-in to the study site, subjects will be advised not to share their study information with other subjects.

16. Data Collection, Retention, and Monitoring

16.1 Data Collection Instruments

All staff at participating clinical sites will adhere to good documentation practices. Data will be entered into eCRFs using source document data. Source documents may include but are not limited to laboratory data, recorded data from automated instruments, medical progress notes, and email correspondence.

16.2 Data Management Procedures

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

All procedures for 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 EDC system directly. The study database will be updated in accordance with the resolved queries, and all changes to the study database will be documented.

16.4 Database Lock/Disclosure of Randomization Code

There will be 2 database locks for the double-blind treatment period of the study:

- A provisional database lock after all subjects complete the Day 169 study visit to allow for the analysis of safety and efficacy data through Day 169.
- A final database lock after all subjects complete the study to allow for the analysis of any safety data collected after Day 169.

For each database lock, applicable EDC data will be locked in order to protect write access after the following preconditions are fulfilled:

- All subjects have completed their participation in the double-blind portion of the study.
- 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 authorization to lock the database is 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 provisional database lock is complete. After the provisional database lock, the randomization code will be made available to a restricted number of individuals at Allakos who are involved in the data analysis. The study will remain blinded to the study sites and Allakos Medical Monitors, Allakos Study Monitors, and Allakos Clinical Data Management until after the final database lock.

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 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/Institutional Review Board Documents
- Drug Accountability
- Correspondence

- Medical Reports
- Subject 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 and remote monitoring and/or auditing of all appropriate study documentation. Due to the coronavirus pandemic, some monitoring may be performed remotely rather than on site.

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), Institutional Review Board (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 subjects. Written approval of a protocol amendment is not required prior to implementation of changes to the protocol that eliminate immediate hazard to the subject; however, approval must be obtained as soon as possible thereafter. Any protocol amendments must also be signed by the Investigator.

17.2 Independent Ethics Committee/Institutional Review Board

The protocol and ICF will be reviewed and approved by the Independent Ethics Committee (IEC) and/or Institutional Review Board (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 IEC/IRB in accordance with the standard operating procedures and policies of the IEC/IRB, and the Investigator will keep the IEC/IRB informed as to the progress of the study. The Investigator will obtain assurance of IEC/IRB compliance with regulations.

Any documents that the IEC/IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, ICF, information concerning subject recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IEC/IRB. The IEC/IRB written unconditional approval of the study protocol and the ICF will be in the possession of the Investigator before the study is initiated. The IEC/IRB 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 the exact protocol title and number and should identify the documents reviewed and the date of review.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may adversely affect the safety of the subjects or the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.3 Informed Consent Form

Prior to study enrollment, all subjects must consent to participate. In accordance with ICH GCP Guideline E6, subjects should be asked whether they would like their primary care physician notified of their study participation. If yes, the physician will be notified in writing. Otherwise, the subject should sign a form stating that he/she does not wish to disclose such information. The process of obtaining informed consent will comply with all federal regulations, ICH requirements, and local laws.

The Investigator or a designee will review the study and the ICF with each potential subject. 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 subject. The Investigator or designee and the subject must both sign and date the ICF after review and before the subject can participate in the study. The subject 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 subject 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 subject is otherwise entitled.

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

17.4 Publications

The preparation of manuscripts containing the study results and submittal for publication shall be in accordance with a process determined by mutual written agreement among the study Sponsor and respective site. The publication or presentation of any study results shall comply with all applicable privacy laws including but not limited to the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

17.5 Clinical Study Registration

This clinical study is registered on the Clinical Trial Registry Website, www.ClinicalTrials.gov, as NCT #04322708.

17.6 Payment to Subjects

All subjects may be compensated for participating in this study in accordance with the payment amounts per study day stated in the subject's signed ICF approved by the IRB. If the subject is discontinued from the study prior to the last study visit, the subject will be compensated for each completed study visit on a pro rata basis, as stated in the subject's ICF. Subjects 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 form, the Investigator agrees to:

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

2) Personally conduct or supervise the study.

3) Ensure that the requirements relating to obtaining informed consent and IEC/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 subjects or others (to include amendments and IND safety reports).

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

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

Abonia J, Blanchard C, Buckmeier-Butz B, Rainey H, Collins M, Stringer K, et al. Involvement of mast cells in eosinophilic esophagitis. Journal of Allergy and Clinical Immunology, 2010;126:140–49.

Arias A, González-Cervera J, Tenias J, Lucendo A. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: A systematic review and meta-analysis. Gastroenterology, 2014;136:1639–48.

Assa'ad A, Gupta S, Collins M, Thomson M, Heath A, Smith D, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. Gastroenterology, 2011;141:1593-1604.

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;39:317–24.

Clayton F, Fang J, Gleich G, Lucendo A, Olalla J, Vinson L, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. Gastroenterology, 2014;147:602–09.

Collins M, Capocelli K, Yang G. Eosinophilic gastrointestinal disorders pathology. Frontiers in Medicine, 2018;4:261.1–8.

Dellon E. Epidemiology of eosinophilic esophagitis. Gastroenterol Clin North Am, 2014;43:201–18.

Dellon E, Speck O, Woodward K, Covey S, Rusin S, Gebhart J, et al. Markers of eosinophilic inflammation for diagnosis of eosinophilic esophagitis and proton pump inhibitor-responsive esophageal eosinophilia: A prospective study. Clin Gastroenterol Hepatol, 2014;12:2015–22.

Dellon E, Veerappan R, Selitsky S, Parker J, Higgins L, Beitia R, et al. A gene expression panel is accurate for diagnosis and monitoring treatment of eosinophilic esophagitis in adults. Clin Transl Gastroenterol, 2017;8:e74.1–8.

Dellon E, Liacouras C, Molina-Infante J, Furuta G, Spergel J, Zevit N, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE Conference. Gastroenterology, 2018;155:1022–33.

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

Furuta G, Atkins F, Lee N, Lee J. Changing roles of eosinophils in health and disease. Ann Allergy Asthma Immunol, 2014;113:3-8.

Furuta G, Katzka D. Eosinophilic Esophagitis. N Engl J Med, 2015;373:1640-48.

Guerin L, Stroup W. A simulation study to evaluate PROC MIXED analysis of repeated measures data. Conference on Applied Statistics in Agriculture, 12th annual conference proceedings, 2000.

Hirano I, Collins M, Assouline-Dayan Y, Evans L, Gupta S, Schoepfer A, et al. RPC4046, a monoclonal antibody against IL13, reduces histologic and endoscopic activity in patients with eosinophilic esophagitis. Gastroenterology, 2019;156:592–603.

Hirano I, Schoepfer A, Comer G, Safroneeva E, Meltzer B, Falk G. A randomized, double-blind, placebo-controlled trial of a fluticasone propionate orally disintegrating tablet in adult and adolescent patients with eosinophilic esophagitis: A Phase 1/2A safety and tolerability study. Gastroenterology, 2017;152:S195.

Hudgens S, Evans C, Phillips E, Hill M. Psychometric validation of the Dysphagia Symptom Questionnaire in patients with eosinophilic esophagitis treated with budesonide oral suspension. Journal of Patient-Reported Outcomes, 2017;1:3.1–11.

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. The American Journal of Gastroenterology, 2013;108:308–328.

Konikoff M, Noel R, Blanchard C, Kirby C, Jameson S, Buckmeier B, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. Gastroenterology, 2006;131:1381-91.

Lucendo A, Arias Á, González-Cervera J, Yagüe-Compadre J, Guagnozzi D, Angueira T, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. J Allergy Clin Immunol, 2013;131:797–804.

Markowitz J, Jobe L, Miller M, Frost C, Laney Z, Eke R. Safety and efficacy of reslizumab for children and adolescents with eosinophilic esophagitis treated for 9 years. J Pediatr Gastroenterol Nutr, 2018;66:893–97.

Molina-Infante J, Bredenoord A, Cheng E, Dellon E, Furuta G, Gupta S, et al. Proton pump inhibitor-responsive oesophageal eosinophilia: An entity challenging current diagnostic criteria for eosinophilic esophagitis. Gut, 2016;65:524–31.

Philpott H, Nandurkar S, Royce S, Thien F, Gibson P. A prospective open clinical trial of a proton pump inhibitor, elimination diet and/or budesonide for eosinophilic oesophagitis. Aliment Pharmacol Ther, 2016;43:985–93.

Reed C, Fan C, Koutlas N, Shaheen N, Dellon E. Food elimination diets are effective for long-term treatment of adults with eosinophilic oesophagitis. Aliment Pharmacol Ther, 2017;46:836–44.

Rothenberg M, Wen T, Greenberg A, Alpan O, Enav B, Hirano I, et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. J Allergy Clin Immunol, 2014;135:500–07.

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.

Spergel J, Rothenberg M, Collins M, Furuta G, Markowitz J, Fuchs III G, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. Journal of Allergy and Clinical Immunology, 2012;129:456–63.

Straumann A, Conus S, Grzonka P, Kita H, Kephart G, Bussmann C, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: A randomised, placebo-controlled, double-blind trial. Gut, 2010;59:21–30.

Straumann A, Katzka D. Diagnosis and treatment of eosinophilic esophagitis. Gastroenterology, 2018;154:346–59.

Syed A, Andrews C, Shaffer E, Urbanski S, Beck P, Storr M. The rising incidence of eosinophilic esophagitis is associated with increasing biopsy rates: A population-based study. Aliment Pharmacol Ther, 2012;36:950–58.

Warners M, Oude N, de Wijkerslooth L, Smout A, Bredenoord A. The natural course of eosinophilic esophagitis and long-term consequences of undiagnosed disease in a large cohort. Am J Gastroenterol, 2018;113:836–44.

19. Appendices

19.1 Appendix 1: Dysphagia Symptom Questionnaire (Paper and Electronic Versions)

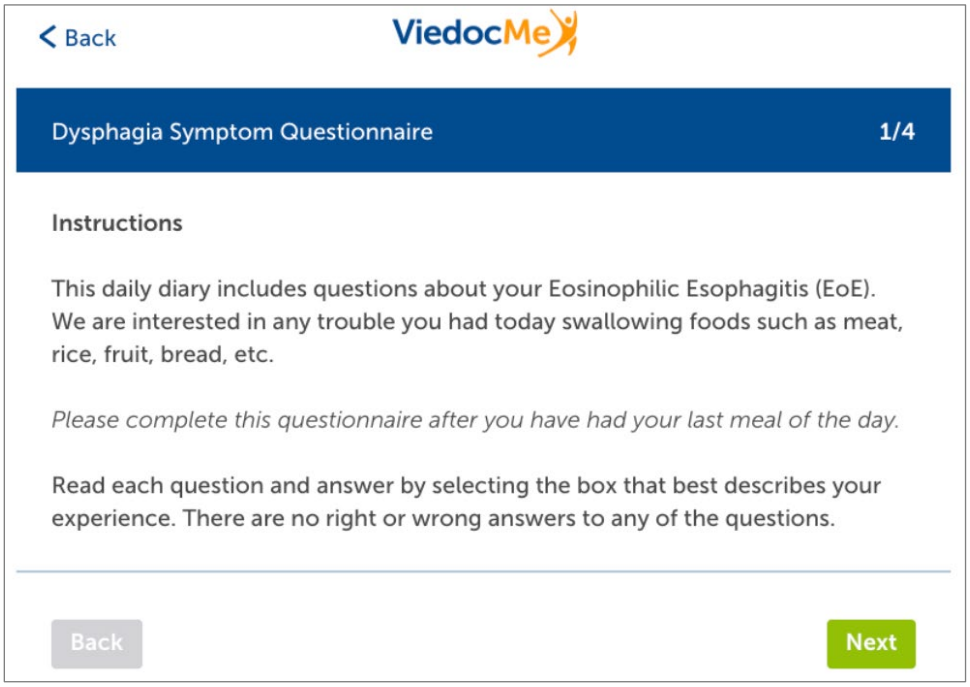
Patient ID: _____ - _____ - _____

Date: _____

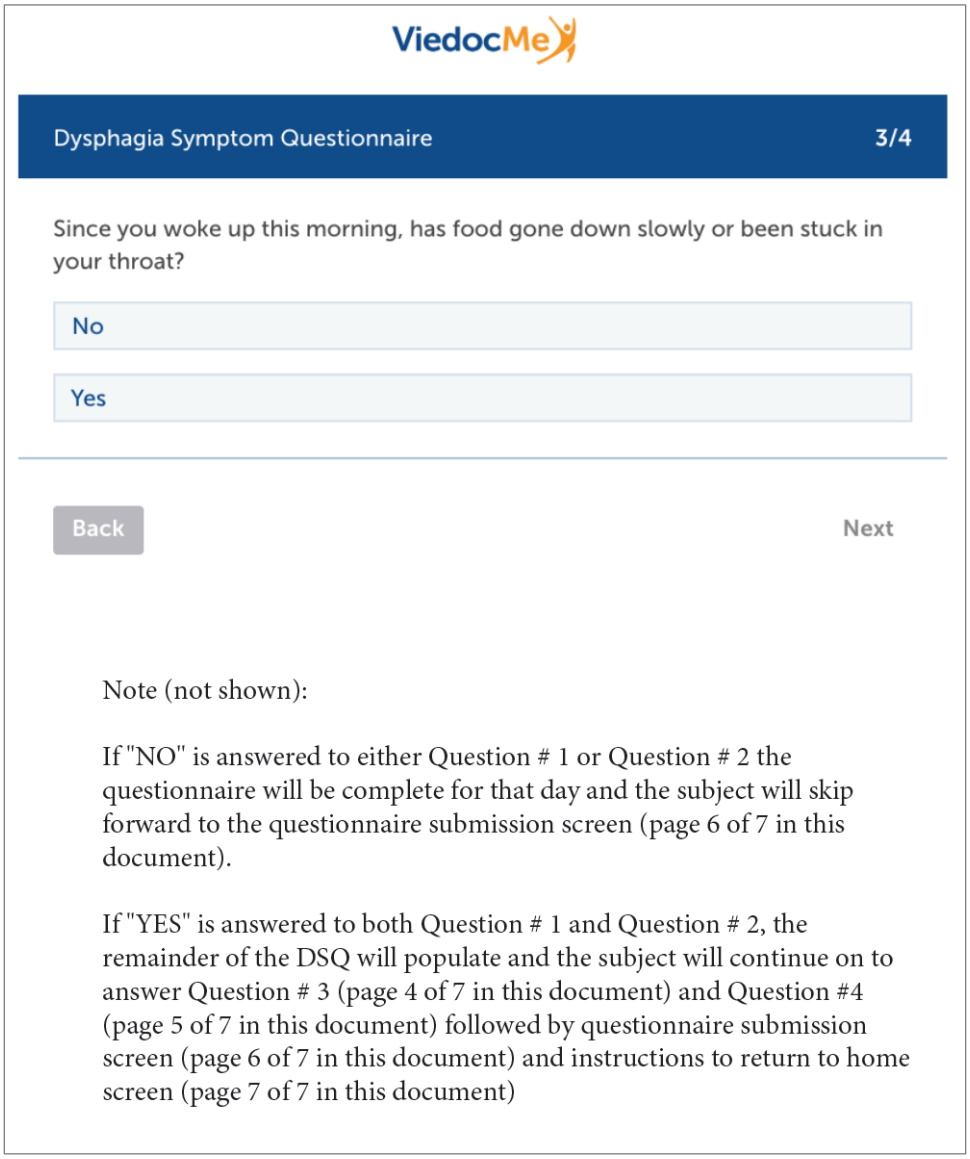
Dysphagia Symptom Questionnaire (DSQ)	
Instructions This daily diary includes questions about your Eosinophilic Esophagitis (EoE). We are interested in any trouble you had today swallowing foods such as meat, rice, fruit, bread, etc. *Please complete this questionnaire after you have had your last meal of the day.* Read each question and answer by selecting the box that best describes your experience. There are no right or wrong answers to any of the questions.	
Question #1: During the past 24 hours, did you eat solid food?	☐ No ☐ Yes
Question #2: During the past 24 hours, has food gone down slowly or been stuck in your throat?	☐ No ☐ Yes
If you answered "Yes" to Questions 1 and 2, please proceed to answer Questions 3 and 4.	
Question #3: For the most difficult time you had swallowing food today (during the past 24 hours), did you have to do anything to make the food go down or to get relief?	☐ No, it got better or cleared up on its own ☐ Yes, I had to drink liquid to get relief ☐ Yes, I had to cough and/or gag to get relief ☐ Yes, I had to vomit to get relief ☐ Yes, I had to seek medical attention to get relief
Question #4: The following question concerns the amount of pain you have experienced when swallowing food: What was the worst pain you had while swallowing food during the past 24 hours?	☐ None, I had no pain ☐ Mild ☐ Moderate ☐ Severe ☐ Very Severe

Allakos, Inc. Dysphagia Symptom Questionnaire v2.0

19.1 Appendix 1: Dysphagia Symptom Questionnaire cont.



19.1 Appendix 1: Dysphagia Symptom Questionnaire cont.

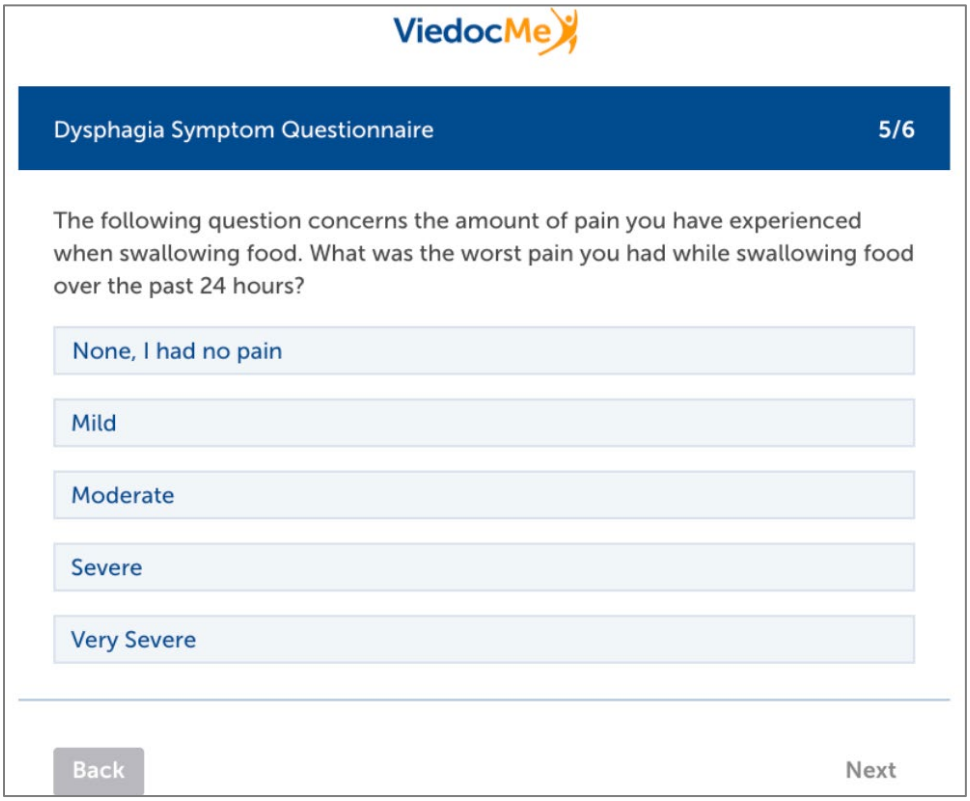


Note (not shown):

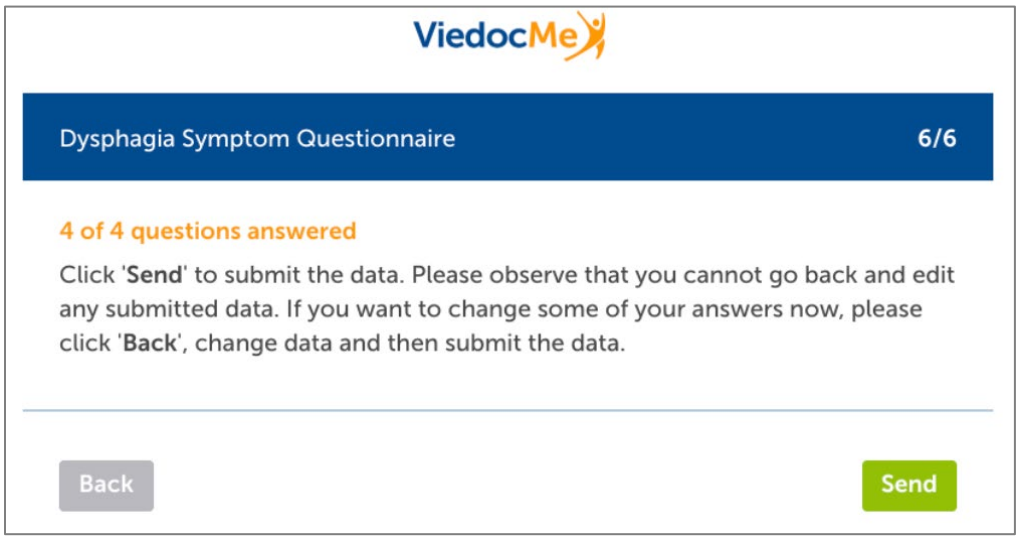
If "NO" is answered to either Question # 1 or Question # 2 the questionnaire will be complete for that day and the subject will skip forward to the questionnaire submission screen (page 6 of 7 in this document).

If "YES" is answered to both Question # 1 and Question # 2, the remainder of the DSQ will populate and the subject will continue on to answer Question # 3 (page 4 of 7 in this document) and Question #4 (page 5 of 7 in this document) followed by questionnaire submission screen (page 6 of 7 in this document) and instructions to return to home screen (page 7 of 7 in this document)

19.1 Appendix 1: Dysphagia Symptom Questionnaire cont.



19.1 Appendix 1: Dysphagia Symptom Questionnaire cont.



19.2 Appendix 2: Solid Food Question (Paper Version)

Patient ID: _____ - _____ - _____

Date: _____

Solid Food Question	
Instructions You are being asked this question because you answered "No" to Question #1 of the Dysphagia Symptom Questionnaire (DSQ). *Please answer this question immediately after you have completed the DSQ.*	
Question: Was EoE the primary reason that you did not eat solid food during the past 24 hours?	☐ No ☐ Yes

Allakos, Inc. Solid Food Question v2.0

CCI

[redacted]

CCI

[redacted]

19.5 Appendix 5: EG/EoD PRO Questionnaire (Paper Version)

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	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐ 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

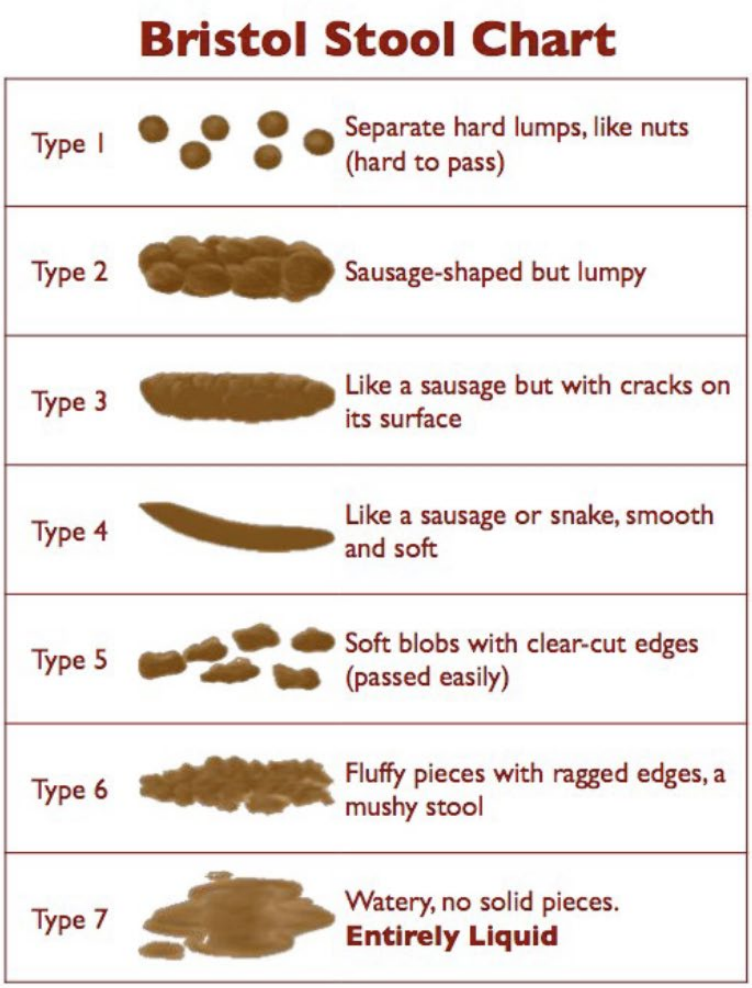
v 14Mar2020 Page **1** of **3**

19.5 Appendix 5: EG/EoD PRO Questionnaire cont.

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

v 14Mar2020 Page **2** of **3**

19.5 Appendix 5: EG/EoD PRO Questionnaire cont.



v 14Mar2020 Page **3** of **3**

©2000, the Rome Foundation, Inc.
For any information on the use of the BSFS, please contact Mapi Research Trust, Lyon, France. Internet: **https://eprovide.mapi-trust.org**

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

Thank you for completing these questions!

CCI

19.7 Appendix 7: 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 the Screening Period.

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 EoE <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 EoE? 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 EoE? Yes ☐ No ☐

If Yes, please describe: _____

_____

19.8 Appendix 8: Common Terminology Criteria for Adverse Events (Version 5.0)

Common Terminology Criteria for Adverse Events (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

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

Example of Grading for Laboratory Abnormalities

Adverse Event	Grade				
	1	**2**	**3**	**4**	**5**
Growth hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	–	–	–
Definition: A finding based on laboratory test results that indicate abnormal levels of growth hormone in biological specimen.					
Haptoglobin decreased	<LLN	–	–	–	–
Definition: A finding based on laboratory test results that indicate a decrease in levels of haptoglobin in a blood specimen.					
Hemoglobin increased	Increase in >0–2 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 x ULN and asymptomatic	>2.0–5.0 × ULN with signs or symptoms; >5.0 x 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.					

19.9 Appendix 9: EGD Histology

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

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

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

Biopsies will be obtained from the following:

- **Esophagus**
  - 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 per hpf in at least one esophageal site will be considered diagnostic of eosinophilic esophagitis (EoE).
- **Stomach**
  - A set of 4 specimens from separate areas of the gastric antrum (2–5 cm proximal to the pylorus)
  - A set of 4 specimens from separate areas of the gastric corpus (two from the proximal lesser curvature and two from the greater curvature)
  - Up to 2 extra specimens may be collected if there are any additional areas of interest

  A count of ≥30 eosinophils per hpf in at least 5 hpf will be considered diagnostic of eosinophilic gastritis (EG).
- **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

  A count of ≥30 eosinophils per hpf in at least 3 hpf will be considered diagnostic of eosinophilic duodenitis (EoD).

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

19.9 Appendix 9: EGD Histology cont.

The following will be reported for esophageal biopsies:

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

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

- Eosinophilic microabscesses
- Eosinophilic degranulation
- Basal zone hyperplasia
- Spongiosis
- Subepithelial tissue present (Y/N)
- Lamina propria fibrosis (grade only if subepithelial tissue is present)

The following will be reported for gastric biopsies:

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

The following will be reported for duodenal biopsies:

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

19.10 Appendix 10: 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)

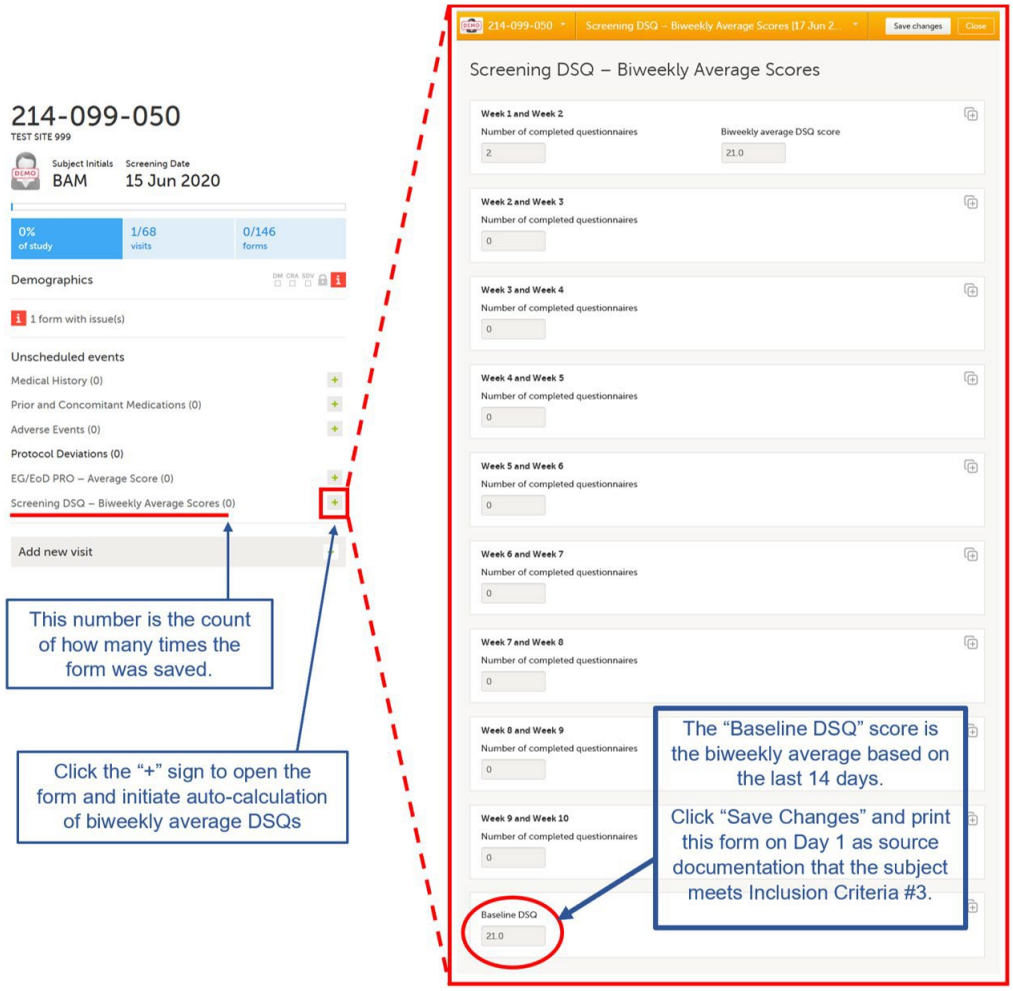
19.11 Appendix 11: Baseline DSQ and Biweekly Mean DSQ Calculation

Inclusion Criterion #3: Baseline DSQ (biweekly mean DSQ) score of ≥12 from the last 2 weeks of screening (the 14 days prior to the first dose) per the validated algorithm in Appendix 11.

If the screening period daily questionnaires were all completed electronically, use the Viedoc EDC "Screening DSQ – Biweekly Average Scores" CRF to confirm eligibility because the baseline DSQ (the biweekly mean DSQ for the 14 days prior to the first dose) is calculated automatically per the following validated algorithm.

To confirm that the subject meets Inclusion Criterion #3, the Study Coordinator must:

1) Click the "+" next to the "Screening DSQ – Biweekly Average Scores" CRF on Day 1.
2) Review "Baseline DSQ" field at the bottom (biweekly mean DSQ over the past 14 days).
3) Click "Save Changes" each time in order to save the data as of that date.



19.11 Appendix 11: Baseline DSQ and Biweekly Mean DSQ Calculation cont.

If using the EDC system's automated calculation is not possible for the purpose of analyzing the biweekly mean DSQ for study endpoints, use the validated scoring algorithm and methods shown below.

The Dysphagia Symptom Questionnaire was validated with the following scoring algorithm:

$$DSQ\ score = \frac{(sum\ of\ points\ from\ questions\ 2\ and\ 3\ from\ daily\ DSQ\ diary) \times 14\ days}{number\ of\ diary\ days\ reported\ with\ non\text{-}missing\ data}$$

Table 1 The Dysphagia Symptom Questionnaire (version 4.0) and score for each response option[a]

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

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

19.12 Appendix 12: Open-Label Extended Dosing Period (Optional)

19.12.1 Summary of the Open-Label Extended Dosing Period

Subjects who complete the double-blind, placebo-controlled treatment period (including the Day 169 study visit) and meet the open-label extended dosing eligibility criteria will be given the option to receive 6 doses of AK002 through the Open-Label Extended Dosing Period (OLE).

On Day 176 (±3 days), eligible subjects participating in the OLE period will begin following the OLE Schedule of Events (Table 5) and will no longer follow the Schedule of Events in Table 1. The Extended Dosing Period is summarized as follows:

- The Investigator will evaluate whether the subject is eligible for OLE. If eligible, the subject will be given the option to participate in the OLE period and receive 6 doses of open-label AK002.
- On Day 176 (±3 days), eligible subjects who choose to participate in the OLE period will begin following the OLE Schedule of Events (Table 5).
- 12–24 hours prior to the first open-label AK002 infusion only, subjects will self-administer oral prednisone premedication (40 mg if body weight is <40 kg, 60 mg if body weight is ≥40 kg and <60 kg, or 80 mg if body weight is ≥60 kg).
- OLE subjects will receive 6 doses of open-label AK002 administered on Days 176 (±3), 204 (±3), 232 (±3), 260 (±3), 288 (±3), and 316 (±3). The first open-label AK002 infusion will be given at a dose of 1 mg/kg. For subsequent open-label AK002 infusions on Days 204 (±3), 232 (±3), 260 (±3), 288 (±3), and 316 (±3), each infusion may be given at a dose of either 1 mg/kg or 3 mg/kg at the discretion of the Investigator.
- Subjects will remain at the site for at least 1 hour of observation after each dose. In the event of an IRR, the subject may require prolonged observation (>1 hour or until the symptoms resolve), as per Investigator discretion.
- Subjects will be followed for approximately 8 weeks after the last dose. Follow-up visits will occur on Day 344 (±7) and Day 372 (±7).
- If absolute lymphocyte and/or eosinophil counts have not recovered by the OLE Day 372 visit, subjects will return approximately every 28 days for extended follow-up until counts have recovered.

19.12.2 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 in subjects with active EoE. The Medical Monitor will review OLE period data relating to safety and tolerability throughout the course of open-label extended dosing.

19.12.3 OLE Eligibility Criteria

Following completion of the randomized, double-blind, placebo-controlled treatment period (including the Day 169 visit), eligible subjects will have the option to receive 6 doses of open-label AK002 through participation in the OLE period.

Subjects who are not eligible for OLE, or who choose not to participate in the OLE period, will remain on study and continue to follow the Schedule of Events (Table 1).

19.12.3.1 OLE Inclusion Criteria

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

1) Subject completed the randomized, double-blind, placebo-controlled treatment period and the Day 169 visit.
2) Subject is willing and able to comply with the OLE period Schedule of Events (Table 5), including receiving the first open-label AK002 infusion at the Day 176 (±3 days) visit.
3) Subject demonstrates continued eligibility per applicable inclusion criteria (Section 7.3) and exclusion criteria (Section 7.4) of the protocol. “Screening” in Section 7 refers only to the screening period completed prior to enrollment in the double-blind treatment period of the study and is not applicable to the OLE period.

19.12.3.2 OLE Exclusion Criteria

Subjects 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 subject, in the opinion of the Investigator.
2) Any other reason that, in the opinion of the Investigator or Medical Monitor, makes the subject unsuitable for participation in the OLE period.

19.12.4 OLE Treatment

Formulation, storage, preparation, and administration of the open-label AK002 drug product for OLE will be consistent with Sections 9.1, 9.3–9.8, and the AK002-014 Pharmacy Manual.

Twelve to 24 hours prior to the first open-label AK002 infusion only, all subjects will self-administer oral prednisone premedication at a dose of 40 mg if body weight is <40 kg, 60 mg if body weight is ≥40 kg and <60 kg, or 80 mg if body weight is ≥60 kg. This dose of prednisone premedication should be recorded in the Concomitant Medications CRF of both the AK002-014 treatment period database and the AK002-014 OLE period database.

The first OLE infusion of AK002 will be administered at a dose of 1 mg/kg over ≥4 hours on Day 176 (±3 days). At the discretion of the Investigator, either the 1 mg/kg or the 3 mg/kg dose may be administered for each subsequent infusion on Days 204 (±3), 232 (±3), 260 (±3), 288 (±3), and 316 (±3). Depending on the subject's tolerance per the Infusion Rate Schedules in the AK002-014 Pharmacy Manual, the second infusion can be given over ≥3 hours and the third, fourth, fifth, and sixth infusions can be given over ≥2 hours. If the infusion is slowed or interrupted, the infusion must be completed within 8 hours of preparation (prior to expiry).

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

19.12.5 OLE Procedures and Guidelines

Apart from differences in the Schedule of Events beginning at Day 176 (±3 days), 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, AE reporting, withdrawal criteria and stopping rules, data collection and management, and ethical and regulatory requirements.

The Investigator will evaluate whether the subject is eligible for the OLE period. On Day 176 (±3 days), eligible subjects that choose to participate in the OLE period will begin following the OLE Schedule of Events (Table 5) and will receive the first open-label AK002 infusion.

Table 5 AK002-014 Open-Label Extended Dosing Period Schedule of Events

Description	Screening	Open-Label Extended Dosing (24 weeks)						OLE Follow-Up (≥8 weeks)[26]	
	No Visit[2]	OLE Dose 1 Day 176 [OLE Day 1] (±3 days)[27]	OLE Dose 2 Day 204 [OLE Day 29] (±3 days)[27]	OLE Dose 3 Day 232 [OLE Day 57] (±3 days)[27]	OLE Dose 4 Day 260 [OLE Day 85] (±3 days)[27]	OLE Dose 5 Day 288 [OLE Day 113] (±3 days)[27]	OLE Dose 6 Day 316 [OLE Day 141] (±3 days)[27]	Day 344 [OLE Day 169] (±3 days)[27]	Day 372 [OLE Day 197] (±7 days) or ET[25]
Evaluate Eligibility for OLE Period[2]	X[2]	X[2]							
DSQ PRO[3]		*Daily through End of Study (or ET)* ---------->							
CCI		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]		X
Baseline Diet Compliance[5]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X
Weight and Vital Signs[6,7]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X
Total Serum IgE[8,9]							X[1]		X
CBC with Differential[8,10]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X
Chemistry[8,11]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X
Pharmacokinetics[8,12]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X
Anti-drug Antibodies[8,13]		X[1]	X[13]	X[13]	X[13]	X[13]	X[13]		X
Exploratory Analysis[8,14]							X[1]		X
Exploratory Safety[8,15]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]		
Urinalysis[8,16]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X
Urine Pregnancy Test[8,17]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]		
Premedication: Prednisone[18]		X[18]							
AK002 Administration[19]		X	X	X	X	X	X		
Post-Dose Observation Period[20]		X	X	X	X	X	X		
Symptom-Directed Physical Exam[21]		X	X	X	X	X	X	X	X
EGD with Biopsy Collection[22]								X	X (ET only)[25]
EREFS Scoring during EGD[23]								X	X (ET only)[25]
Concomitant Medications		X	X	X	X	X	X	X	X
Adverse Events[24]		X	X	X	X	X	X	X	X

ADA: Anti-drug Antibody
CBC: Complete Blood Count
DSQ: Dysphagia Symptom Questionnaire
ET: Early Termination
PK: Pharmacokinetics

Table 5 Notes

1) Refer to assessment footnote for specific timing (e.g., predose, during infusion, postdose).
2) The Investigator will evaluate whether the subject is eligible for the OLE period per Section 19.12.3. On Day 176 (±3 days), eligible subjects that choose to participate in the OLE period will begin following the OLE Schedule of Events and will receive the first open-label AK002 infusion.
3) Subjects should complete the DSQ daily after the last meal of the day. If Question 1 is answered "No," the subject should answer the Solid Food Question (Appendix 2) after the DSQ is completed and submitted. The site is responsible for monitoring compliance and discussing compliance during study visits.
4) CCI should be the first assessment completed by the subject at the beginning of the study visit prior to other assessments.
5) Per Inclusion Criterion #7, subjects should maintain the baseline diet consistently throughout the study. Diet compliance will be discussed during study visits and any variance will be documented.
6) Weight will be measured predose on Days 176, 204, 232, 260, 288, and 316, and Days 344 and 372 (or ET).
7) Vital signs will be measured at all OLE visits. On dosing days (Days 176, 204, 232, 260, 288, and 316), vital signs will be measured predose, 15 minutes (±5 minutes) after infusion start, immediately postdose (within 5 minutes after infusion end), and 1 hour (±5 minutes) postdose. Subject should be at rest for ≥5 minutes before vital signs (systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate) are measured.
8) Please see the Central Laboratory Manual for collection, processing, and shipment instructions. Samples should be shipped on the same day as collection.
9) Blood for total serum IgE will be obtained predose on Day 316 and again on Day 372 (or ET).
10) Blood for CBC with differential will be obtained at all OLE period study visits. On Days 176, 204, 232, 260, 288, and 316, blood will be drawn twice (predose and 1-hour postdose).
11) Blood for chemistry will be obtained at all OLE period study visits. On Days 176, 204, 232, 260, 288, and 316, blood for chemistry will be drawn predose.
12) Blood for PK will be obtained at all OLE period study visits. On Days 176, 204, 232, 260, 288, and 316, blood for PK will be drawn predose.
13) Blood for ADA will be obtained predose on Day 176 and on Day 372 (or ET). For Days 204, 232, 260, 288, and 316, blood for ADA will be obtained only if a suspected immunogenicity-related AE occurs.
14) Blood for exploratory analysis will be obtained predose on Day 316 and on Day 372 (or ET).
15) Blood for exploratory safety analyses will only be obtained within 1–2 hours of symptom onset if an IRR results in infusion interruption or cessation.
16) Urine for urinalysis will be obtained predose on Day 176, as needed (if warranted in the opinion of the Investigator or Subinvestigator), and on Day 372.
17) For females of childbearing potential, urine will be collected, tested, and pregnancy result confirmed predose on Days 176, 204, 232, 260, 288, and 316.

Table 5 Notes cont.

18) The day before the first open-label AK002 dose (12–24 hours prior to the infusion start time), subjects will self-administer oral prednisone premedication at a dose of 40 mg if body weight is <40 kg, 60 mg if body weight is ≥40 kg and <60 kg, or 80 mg if body weight is ≥60 kg. This dose of prednisone premedication should be recorded in the Concomitant Medications CRF of both the AK002-014 treatment period database and the AK002-014 OLE period database.

19) Open-label AK002 will be administered as a single peripheral IV infusion over ≥4 hours on Day 176, over ≥3 hours on Day 204, and over ≥2 hours on Days 232, 260, 288, and 316. Refer to the Pharmacy Manual for detailed administration and infusion rate schedule instructions.

20) Subjects 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 subject may require prolonged observation (>1 hour or until the symptoms resolve), as per Investigator discretion. Subjects will also be instructed to immediately contact the study doctor if any reactions occur after discharge.

21) 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. Symptom-directed physical examinations will be performed if warranted (per the Investigator or designee judgment) and may be performed at any time or multiple times during a visit (predose, during infusion, and/or postdose).

22) An EGD with biopsy collection will be performed on Day 344 (±3 days). EGD biopsies will be collected, processed, and shipped in accordance with Appendix 9, the central laboratory manual, and the histology manual.

23) During the Day 344 EGD, severity will be evaluated using the EoE Reference Score for Endoscopic Abnormalities per the AK002-014 Histology Manual.

24) All AE, including AESI and SAE, will be captured through the entire OLE period until Day 372 (or ET). Adverse events will be assessed and recorded in the CRF of the AK002-014 OLE period database beginning from the start of the first open-label infusion during the Day 176 visit.

25) The ET visit should be conducted 28 (±3) days after the last dose of open-label AK002 or prior to this, if necessary, to ensure compliance with the visit. If ET occurs after the Day 204 study visit and before the Day 344 study visit, then an EGD with biopsy collection must be done 28 (±3) days after the last dose of open-label AK002. If a subject discontinues the study >28 days after the last dose of study drug, the ET visit should be conducted as soon as possible.

26) 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 days (±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.

27) Sites should strive to conduct visits within a ±3 day window, but visits conducted within ±7 days are acceptable and are not considered deviations. Visits conducted ±4-7 days from the target visit date should be minimized as much as possible. Any visit conducted outside of the ±3 day window should receive prior written approval from Allakos.