A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AK002 in Patients with Moderately to Severely Active Eosinophilic Gastritis and/or Eosinophilic Duodenitis (formerly referred to as Eosinophilic Gastroenteritis) Who Have an Inadequate Response with, Lost Response to, or Were Intolerant to Standard Therapies

NCT Number: NCT04322604
IRB Approval Date: 02 Nov 2021
Document Date: 26 Oct 2021

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

# Clinical Research Protocol AK002-016

## A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AK002 in Patients with Moderately to Severely Active Eosinophilic Gastritis and/or Eosinophilic Duodenitis (formerly referred to as Eosinophilic Gastroenteritis) Who Have an Inadequate Response with, Lost Response to, or Were Intolerant to Standard Therapies

| | | |
|---|---|---|
| Protocol Number | AK002-016 | |
| Version and Date | Original | 30 September 2019 |
| | Amendment 1 | 18 March 2020 |
| | Amendment 2 | 07 August 2020 |
| | Amendment 3 | 20 April 2021 |
| | **Amendment 4** | **26 October 2021** |
| Investigational Product | AK002 (lirentelimab) | |
| Study Phase | 3 | |
| Sponsor | Allakos Inc., 975 Island Drive, Suite 201<br>Redwood City, CA 94065 USA | |
| Medical Monitor | Name: PPD MD<br>Telephone: PPD<br>Email: PPD | |

**Approval:** PPD

26-Oct-2021 | 14:40 PDT

PPD MD, MBA — Date

PPD

### *Confidentiality Statement*

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

# Investigator Protocol Agreement

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

**Protocol Number:** AK002-016

**IND:** 135158

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

**Original Protocol:** 30 September 2019

**Amendment 1:** 18 March 2020

**Amendment 2:** 07 August 2020

**Amendment 3:** 20 April 2021

**Amendment 4:** **26 October 2021**

**Investigator Printed Name:** _____

**Investigator 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 event(s) |
| AESI | Adverse event(s) of special interest |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical Classification System |
| BMI | Body mass index |
| CBC | Complete blood count |
| CDC | Complement-dependent cytotoxicity |
| CDF | Cumulative distribution function |
| CFR | Code of Federal Regulation |
| CI | Confidence interval |
| cm | Centimeter |
| CMH | Cochran-Mantel-Haenszel (test) |
| COVID-19 | **C**oronavirus disease of 2019 |
| CS | Clinically significant |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CU | Chronic Urticaria |
| eCDF | empirical Cumulative Distribution Function |
| ECG | Electrocardiogram(s) |
| eCRF | Electronic Case Report Form |
| EG | Eosinophilic gastritis |
| EGD | Esophago-gastro-duodenoscopy |
| EGID | Eosinophilic gastrointestinal disorders |
| EGPA | Eosinophilic granulomatosis with polyangiitis |
| ELISA | Enzyme-linked immunosorbent assay |
| EoD | Eosinophilic duodenitis (formerly referred to as eosinophilic gastroenteritis) |
| EoE | Eosinophilic esophagitis |

| | |
|---|---|
| EOS | End of study |
| ET | Early Termination |
| FDA | Food and Drug Administration |
| FSH | Follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GGT | Gamma-glutamyl transferase |
| GI | Gastrointestinal |
| GLP | Good Laboratory Practice |
| hCG | human Chorionic Gonadotropin |
| HEENT | Head, eyes, ears, nose, and throat |
| HES | Hypereosinophilic Syndrome (HES) |
| HIPAA | Health Insurance Portability and Accountability Act |
| hpf | High power field |
| ICE | Intercurrent events |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation |
| iDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IgE | Immunoglobulin E |
| IgG1 | Immunoglobulin G1 |
| IND | Investigational New Drug (application) |
| IP | Investigational product |
| IRB | Institutional Review Board |
| IRR | Infusion-Related Reaction |
| IRT | Interactive Response Technology |
| ISM | Indolent systemic mastocytosis |
| ITIM | Immunoreceptor Tyrosine-based inhibitory motif |
| ITT | Intent to treat |
| IV | Intravenous |
| kg | Kilogram |
| LLN | Lower limit of normal |
| LSM | Least squares mean |
| MAR | Missing at random |

| | |
|---|---|
| MCS | Mental component score |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |
| MI | Multiple imputation |
| MITT | Modified Intention-to-Treat |
| mL | Milliliter |
| mM | Millimolar |
| MMRM | Mixed model for repeated measures |
| MNAR | Missing not at random |
| MTD | Maximum tolerated dose |
| NaCl | Sodium chloride |
| NCI | National Cancer Institute |
| NCS | Not clinically significant |
| NOAEL | No-observed-adverse-effect level |
| O&P | Ova and Parasite (test) |
| OR | Odds ratio |
| OTC | Over The Counter |
| PCP | Primary care physician |
| PCS | Physical component score |
| PD | Pharmacodynamics |
| PDF | Probability distribution function |
| PE | Physical examination |
| PEF | Peak expiratory flow |
| CCI | [redacted] |
| CCI | [redacted] |
| PID | Patient identification number |
| PK | Pharmacokinetic(s) |
| PP | Per Protocol |
| PPI | Proton pump inhibitor |
| PRO | Patient reported outcome |
| SAE | Serious adverse event(s) |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |

| | |
|---|---|
| SE | Standard error |
| CCI | [redacted] |
| Siglec | Sialic acid-binding, immunoglobulin-like lectin |
| SOC | System organ class |
| TEAE | Treatment-emergent adverse event(s) |
| TEAESI | Treatment-emergent adverse event(s) of significant interest |
| TNF | Tumor necrosis factor |
| TSS | Total Symptom Score |
| UBT | Urea Breath Test |
| ULN | Upper limit of normal |
| USP | United States Pharmacopeia |
| WHODD | World Health Organization Drug Dictionary |
| w/v | Weight/volume |

## 1. Protocol Synopsis

| | |
|---|---|
| **Study Title** | A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AK002 in Patients with Moderately to Severely Active Eosinophilic Gastritis and/or Eosinophilic Duodenitis (formerly referred to as Eosinophilic Gastroenteritis) Who Have an Inadequate Response With, Lost Response to, or Were Intolerant to Standard Therapies |
| **Sponsor** | Allakos Inc., 975 Island Drive, Suite 201, Redwood City, CA 94065 USA |
| **Number of Sites** | Approximately 60 clinical centers |
| **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).<br><br>Siglec-8 has a restricted tissue distribution, expressed selectively on the surface of mature eosinophils and mast cells, but not in early precursors of these cell populations. In blood, binding of AK002 to Siglec-8 induces antibody-dependent cellular cytotoxicity (ADCC) against eosinophils, leading to rapid and sustained depletion of these cells from the circulation. In the tissue, AK002 induces direct apoptosis of eosinophils and inhibition of mast cells. |
| **Clinical Background** | AK002, administered as an intravenous infusion, has been previously tested in healthy volunteers and in patients with indolent systemic mastocytosis (ISM), chronic urticaria (CU), severe allergic conjunctivitis (AC), mast cell gastritis, and eosinophilic gastritis (EG) and/or eosinophilic duodenitis (EoD), which was referred to as eosinophilic gastroenteritis (EGE) in previous studies. Multiple doses of 3 mg/kg have been given to patients with ISM, CU, AC, EG, and/or EoD. In these studies, patients reported improvements in disease symptoms, with AK002 pharmacodynamic (PD) activity being observed for prolonged periods of time and pharmacokinetic (PK) parameters demonstrating a half-life amenable to administration every 4 weeks.<br><br>To date, healthy volunteers and patients with ISM, CU, severe AC, EG/EoD, EoE, and mast cell gastritis have been enrolled in clinical studies. In general, AK002 has been well tolerated. The most common treatment-emergent adverse events (TEAE) observed were infusion-related reaction (IRR). Most IRR were mild to moderate and resolved on their own, with no treatment required; IRR that were serious resolved within approximately 24 hours. Transient lymphopenia was observed after infusion of AK002 but was not associated with any clinical consequence, and lymphocytes recovered within 24 hours. A sustained depletion of eosinophils was observed that is consistent with the mechanism of action of AK002.<br><br>In the randomized, double-blind, placebo-controlled, Phase 2 study of AK002 in 65 patients with EG and/or EoD, patients were randomized to receive monthly doses of placebo, low dose AK002 (0.3, 1, 1, and 1 mg/kg), or high dose AK002 (0.3, 1, 3, and 3 mg/kg) in a 1:1:1 ratio. |

| | |
|---|---|
| **Clinical Background cont.** | All primary and secondary endpoints were met in the study. There was a 97% and 92% mean reduction in eosinophils in the stomach/duodenum at the high and low doses, respectively, versus 10% increase for patients on placebo ($p<0.0001$).<br><br>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 and 49% in the low dose group versus 24% reduction in placebo ($p=0.0012$ and $p=0.015$, respectively). Improvement in symptoms was observed within 24 hours of the first dose of study drug. In addition, 70% of high dose treated patients and 68% of low dose treated patients were treatment responders (defined as >30% improvement in TSS and >75% reduction from baseline in tissue eosinophils) versus 5% for placebo treated patients ($p<0.0001$).<br><br>Approximately 40% of patients had concomitant eosinophilic esophagitis (EoE). In those patients, a mean reduction of 95% of eosinophils/high powered field (hpf) in esophageal biopsies for AK002 was observed versus no change for placebo. Also, 13 of 14 AK002-treated patients (93%) were histologic responders as defined by ≤6 eosinophils/hpf versus 1 of 9 placebo-treated patients (11%). Dysphagia improved by 53% in AK002-treated patients versus 17% in placebo-treated patients.<br><br>More than 90% of patients in the Phase 2 study elected to continue into a long-term extension study (AK002-003X). In that study, a starting dose of 1 mg/kg was followed by doses of 3 mg/kg. Premedication of 80 mg oral prednisone was administered the day before the first and second doses. Using this premedication regimen, no IRR were reported on the first infusion of AK002 in the extension study. |
| **Target Disease Background and Rationale** | EG and/or EoD (previously referred to as EGE) represent what are traditionally believed to be rare types of eosinophilic gastrointestinal disorders (EGID) that are characterized by chronic, often severe inflammation due to patchy or diffuse infiltration of eosinophils into layers of the stomach, small intestine, or both (Prussin, 2014; Reed, 2015; Zhang, 2017).<br><br>The diagnosis is based on clinical presentation (gastrointestinal symptoms) combined with increased tissue eosinophils in biopsy specimens from the stomach and/or duodenum without any other cause for the eosinophilia. Involvement of the small intestine is typically assessed by performing duodenal biopsies using an esophago-gastro-duodenoscopy (EGD) and has been referred to as eosinophilic gastroenteritis or eosinophilic enteritis though eosinophilic duodenitis (EoD) is more appropriate.<br><br>The gastrointestinal symptoms are believed to be due to the release of inflammatory mediators from activated eosinophils, and likely mast cells. Symptoms that are often severe and debilitating commonly include abdominal pain, nausea, bloating, early satiety, fullness before finishing a meal, abdominal |

| | |
|---|---|
| **Target Disease Background and Rationale cont.** | cramping, vomiting, diarrhea, and weight loss (Alhmoud, 2016; Lopez-Medina, 2015; Mansoor, 2017; Reed, 2015). Jensen (2016) estimated the prevalence of EG and EoD to be 6.3/100,000 and 8.4/100,000, respectively (for patients from 1 to 64 years of age). Mansoor (2017) estimated the overall prevalence of EG to be 5.1/100,000 persons.<br><br>Patients may also have concomitant atopic diseases like food allergy, asthma and atopic dermatitis, which further impacts quality of life and contributes to health care costs. Additionally, 8% to 10% of patients have concomitant EoE (Jensen, 2016).<br><br>There are no FDA-approved treatments for EG or EoD. Current therapies and disease management includes dietary restriction/elimination, proton pump inhibitors (PPI), antihistamines, systemic or swallowed corticosteroids, and occasional off-label use of immunomodulatory biologics (Prussin, 2014; Reed, 2015; Zhang, 2017).<br><br>Proton pump inhibitors have little to no benefit in patients with EG and/or EoD despite reports of providing partial benefit in some patients with EoE (Katz, 2013). Restricted/elemental diets are not effective long-term treatment as they require strict compliance and, in the case of elemental diets, are expensive and are often not reimbursed by insurance. In addition, compliance is very poor and patient quality of life is greatly impacted (Bedell, 2018; Peterson, 2013; Wechsler, 2014). Corticosteroids, systemic or topical, have been shown to provide symptom relief but are not appropriate for long-term treatment due to numerous side effects and associated risks including adrenal insufficiency, bone demineralization, increased chance of infection, osteoporosis, behavioral issues, and weight gain.<br><br>By markedly reducing the number of blood and tissue eosinophils and inhibiting the activation of mast cells, AK002 may be useful in the treatment of patients with EG and/or EoD. This premise is supported by the Phase 2 data with AK002 that shows significant improvements in histology and symptoms in these patients.<br><br>Given there are no approved therapies for these chronic and debilitating diseases, better treatment options are clearly needed to manage EG and EoD. |
| **Rationale for Dose Selection** | Based on experience with AK002 in healthy volunteers and in patients with ISM, CU, severe AC, and EG/EoD, the proposed AK002 dose regimen of 6 total doses is 1 mg/kg for the first infusion, followed by 5 doses of 3 mg/kg AK002, administered every 4 weeks.<br><br>CCI [redacted] |

| | |
|---|---|
| **Rationale for Dose Selection cont.** | CCI [redacted] |
| **Number of Patients** | Approximately 160 patients with symptomatic EG and/or EoD will be randomized 1:1 to receive 1 of 2 dose regimens in a double-blind fashion:<br>• 6 doses of placebo<br>• AK002 at 1 mg/kg for the first dose followed by 3 mg/kg administered every 4 weeks for 5 subsequent doses.<br><br>The rationale for the number of patients is described under Statistical Analysis. Approximately 90 patients with EG ± EoD will be enrolled, and approximately 70 patients with EoD without EG will be enrolled. |
| **Study Design** | This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of AK002 in patients with EG and/or EoD who have an inadequate response with, lost response to, or were intolerant to standard therapies.<br><br>Patients enrolled in the study will receive 6 infusions of placebo or AK002 administered every 4 weeks and will be followed for 12 weeks after the last dose unless patients elect to enter the optional long-term extension study (AK002-016X).<br><br>Patients will be consented and then screened for up to 45 days prior to Day 1. Patients who meet all eligibility criteria can be enrolled into the study. Patients who do not meet all eligibility criteria at screening, or who qualify at screening but are not enrolled, may be assigned a new patient identification number and rescreened once. Patients rescreened within 30 days of signing the initial consent will not need to sign a new informed consent form (ICF) if no changes have been made to the ICF.<br><br>The study is designed as follows:<br>• An 18 to 45-day screening period with baseline evaluations for study eligibility, including active symptoms of disease (gathered by the patient reported outcome [PRO] questionnaire completed during screening) and EGD with biopsy. |

| | |
|---|---|
| **Study Design cont.** | • Prior EGD and stool sample may be used for eligibility as long as they were done within 30 days of the first screening visit for the AK002-016 study and were performed and centrally assessed as for the AK002-016 study.<br>• If patients meet histology and symptom eligibility criteria, they will be randomized and stratified by the highest weekly TSS of disease activity recorded during the screening period (<28 or ≥28 strata) and whether the patient is EoD-only. The IRT will assign patients 1:1 to receive 6 doses of AK002 or placebo.<br>• Pre-study medications and dietary restrictions should remain unchanged throughout the screening period and throughout the study. Systemic or topical corticosteroids above 10 mg daily prednisone (or the equivalent thereof) will not be allowed, except as an approved premedication prior to infusion or to treat an IRR that occurs during infusion or for unforeseen circumstances when it is deemed to be medically necessary to treat an unrelated medical condition.<br>• Eligible patients will receive the first dose of placebo or AK002 (1 mg/kg) on Day 1, with premedication of 60 mg oral prednisone 12–24 hours prior to the start of the infusion.<br>• If the study drug is well tolerated (no stopping rules being met), patients will receive additional doses of placebo or AK002 (3 mg/kg) on Days 29, 57, 85, 113, and 141. With the exception of Day 1, steroid premedication will only be allowed with the written approval of the Medical Monitor.<br>• Patients will remain at the site for at least 1 hour of observation following the end of the infusion.<br>• An EGD with biopsy will be performed on Day 169 (±3) or 28 (±3) days after last dose of study drug if patient early-terminates.<br>• Daily administration of the PRO Questionnaire for all patients.<br>• Follow-up will occur for 84 (±3) days after the last dose of study drug unless patients decide to enter the long-term extension study. Follow-up visits for patients opting not to enter the extension study will occur on Day 176 (±3), Day 197 (±3), and 225 (±3).<br>• Total study duration is approximately 35–37 weeks. For patients entering the AK002-016X extension study, the total study duration may be as short as 28 weeks.<br>• Patients who satisfactorily complete the randomized double-blind study will have the option to receive AK002 in a separate open-label extension study if all eligibility criteria for the extension study are satisfied. Patients who enroll in the AK002-016X extension study may begin the extension study dosing 1 day after completing the Day 176 visit of this protocol. |

| | |
|---|---|
| **Study Design cont.** | • Patients opting to enter the extension study but who cannot start the extension study 1 day after the Day 176 visit has occurred will remain in the main study until they receive the first dose of study drug in the extension study.<br>• The Day 197 and Day 225 main study visits will occur if the patient does not enroll in the extension study prior to the scheduled date of these visits. A patient enrolling in the AK002-016X study prior to Day 197 will not complete the Day 197 or Day 225 procedures under Protocol AK002-016. A patient not enrolled in the extension study before Day 225 will not be able to enter the extension study. Open-label dosing and follow-up will occur under the extension study. |
| **Primary Objectives** | To evaluate the efficacy and safety of 6 doses of AK002 in patients with moderate-to-severe EG and/or EoD when compared with placebo.<br>Efficacy will be evaluated by co-primary endpoints, namely:<br>1) First co-primary endpoint – Proportion of Tissue Eosinophil Responders at Week 24: A responder is a patient achieving the following eosinophil counts:<br>– EG: Mean eosinophil count ≤4 cells/hpf in 5 highest gastric hpf<br>– EoD: Mean eosinophil count ≤15 cells/hpf in 3 highest duodenal hpf<br>– EG + EoD: Mean eosinophil count ≤4 cells/hpf in 5 highest gastric hpf ***and*** mean eosinophil count ≤15 cells/hpf in 3 highest duodenal hpf<br>2) Second co-primary endpoint: Change in TSS from Baseline to Weeks 23–24 as measured by the PRO questionnaire.<br>The PRO Total Symptom Score (TSS) comprises the following 6 symptoms:<br>– Abdominal pain intensity<br>– Nausea intensity<br>– Fullness before meal intensity<br>– Loss of appetite intensity<br>– Bloating intensity<br>– Abdominal cramping intensity<br>Safety will be evaluated by adverse event (AE) reporting, laboratory safety tests, changes in vital signs, changes in concomitant medication use due to AE, immunogenicity, and other safety parameters. |
| **Secondary Objectives** | To further characterize the efficacy of AK002 in patients with EG and/or EoD as measured by:<br>• Change in tissue eosinophils from Baseline to Week 24.<br>• Proportion of patients achieving a mean eosinophil count ≤1 cell/hpf in 5 highest gastric hpf and/or a mean eosinophil count ≤1 cell/hpf in 3 highest duodenal hpf at Week 24. |

| | |
|---|---|
| **Secondary Objectives cont.** | • Proportion of treatment responders at Week 24. A responder is defined as >30% improvement in TSS ***and*** mean eosinophil count ≤4 cells/hpf in 5 highest gastric hpf and/or mean eosinophil count ≤15 cells/hpf in 3 highest duodenal hpf.<br>• Proportion of patients who achieve ≥50% reduction in TSS from Baseline to Weeks 23–24.<br>• Proportion of patients who achieve ≥70% reduction in TSS from Baseline to Weeks 23–24.<br>• Change in weekly TSS over time. |
| **Exploratory Objectives** | To evaluate the effect of AK002 by comparing AK002 to placebo treatment for the following parameters:<br>• Change from Baseline in CCI [redacted] over time.<br>• Change from Baseline in CCI [redacted] over time.<br>• For patients with CCI [redacted]): Proportion of patients achieving a CCI [redacted] at Week 24.<br>• Change from Baseline in CCI [redacted] over time. |
| **Study Population** | Adult male and female patients with moderate to severe EG and/or EoD with inadequate or loss of response to, or intolerance to standard therapies. |
| **Patient Selection Criteria** | **Inclusion Criteria**<br>Patients are eligible to enroll in the study if all of the following criteria are met:<br>1) Provide written informed consent.<br>2) Male or female aged ≥18 and ≤80 years at the time of signing the informed consent for entry.<br>3) Baseline endoscopic biopsy with ≥30 eosinophils/hpf in 5 hpf in the stomach and/or ≥30 eosinophils/hpf in 3 hpf in the duodenum, as determined by central histology assessment of biopsies collected during the screening EGD, without any other significant cause for the eosinophilia.<br>Prior EGD may be used for eligibility as long as the EGD occurred within 30 days of the first screening visit for the AK002-016 study and was performed and centrally assessed as for the AK002-016 study.<br>4) Completion of at least 4 daily PRO questionnaires per week for a minimum of 3 weeks during screening. |

| | |
|---|---|
| **Patient Selection Criteria cont.** | **Inclusion Criteria cont.**<br>5) A weekly average score of abdominal pain, nausea, or diarrhea ≥3 on the PRO questionnaire (score from 0–10) and a weekly average TSS of ≥10 for at least 2 weeks of screening.<br>6) Patients with inadequate or loss of response to, or who were intolerant to standard therapies for EG/EoD symptoms, which could include PPI, antihistamines, systemic or topical corticosteroids, and/or diet, among others.<br>7) If patient is on pre-existing dietary restrictions, willingness to maintain dietary restrictions throughout the study.<br>8) Willing and able to comply with all study procedures and visit schedule including follow-up visits.<br>9) Female patients must be either post-menopausal for at least 1 year with FSH level >30 mIU/mL at screening or surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months, or if of childbearing potential, have a negative pregnancy test and agree to use dual methods of contraception, or abstain from sexual activity from screening until the end of the study, or for 120 days following the last dose of study drug, whichever is longer.<br>Male patients with female partners of childbearing potential must 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 (e.g., missed or later menstrual period) at any time during study participation.<br>**Exclusion Criteria**<br>Patients will be excluded from the study if they meet any of the following criteria:<br>1) Use of systemic or topical corticosteroids exceeding the equivalent of 10 mg/day of prednisone within 4 weeks prior to the screening visit.<br>2) Change in the dose of corticosteroids (systemic or topical), PPI, leukotrienes, or diet therapy within 4 weeks prior to the screening visit.<br>3) Treatment with any immunosuppressive or immunomodulatory drugs that may interfere with the study within 12 weeks prior to the screening visit.<br>4) Prior exposure to AK002 or known hypersensitivity to any constituent of the study drug.<br>5) Active *Helicobacter pylori* infection, unless treated and confirmed to be negative prior to randomization and histology per repeat EGD and symptoms still qualify for enrollment after treatment. |

| | |
|---|---|
| **Patient Selection Criteria cont.** | **Exclusion Criteria cont.**<br>6) History of inflammatory bowel disease, celiac disease, achalasia, or esophageal surgery.<br>7) History of bleeding disorders and/or esophageal varices considered to be clinically significant by the Investigator.<br>8) Other significant causes of gastric and/or duodenal eosinophilia or eosinophilic granulomatosis with polyangiitis (EGPA).<br>9) Confirmed diagnosis of hypereosinophilic syndrome (HES).<br>10) Women who are pregnant, breastfeeding, or planning to become pregnant while participating in the study.<br>11) Presence of an abnormal laboratory value considered to be clinically significant by the Investigator.<br>12) Any disease, condition (medical or surgical), or cardiac abnormality, which, in the opinion of the Investigator, would place the patient at increased risk.<br>13) History of malignancy, except carcinoma in situ, early stage prostate cancer, or non-melanoma skin cancers. However, patients with cancers that have been in remission for more than 5 years and are considered cured, can be enrolled.<br>14) Treatment for a clinically significant helminthic parasitic infection within 6 months of screening.<br>15) Positive helminthic infection on Ova and Parasite (O&P) test.<br>16) Seropositive for *Strongyloides stercoralis* at screening, except for patients with past but resolved infection.<br>17) Seropositive for HIV or hepatitis at screening, except for vaccinated patients or patients with past but resolved hepatitis, at screening.<br>18) Vaccination with live attenuated vaccines within 30 days prior to initiation of treatment in the study, during the treatment period, or vaccination expected within 5 half-lives (4 months) of study drug administration. All types and formulations of vaccines (including live attenuated vaccines) authorized by FDA or other regulatory authority for the prevention of COVID-19 may be administered before, during, or after this study. The vaccine should not be administered within 7 days prior to and within 7 days after the administration of AK002 so that any side effects caused by either of the 2 medications can be more easily determined.<br>19) Participation in a concurrent interventional study with the last intervention occurring within 30 days prior to study drug administration (or 90 days or 5 half-lives, whichever is longer, for biologic products). |

| | |
|---|---|
| **Patient Selection Criteria cont.** | **Exclusion Criteria cont.**<br>20) Known history of alcohol, drug, or other substance abuse or dependence that is considered by the Investigator to be ongoing and clinically significant.<br>21) Any other reason that in the opinion of the Investigator or the Medical Monitor makes the patient unsuitable for enrollment. |
| **Test Product, Dose, and Administration** | AK002 (CCI [redacted]) and placebo are supplied as sterile liquids and will be diluted with 0.9% NaCl for intravenous (IV) injection. The injection will be administered by IV infusion, as specified in the Pharmacy Manual.<br>AK002 and placebo are formulated in CCI [redacted] pH 6.0, in Water for Injection (WFI).<br>AK002 at a dose of 1 mg/kg or placebo will be prepared according to the patient's body weight and administered on Day 1. Subsequent infusions of AK002 at a dose of 3 mg/kg or placebo according to the patient's body weight will be administered on Day 29 (±3), Day 57 (±3), Day 85 (±3), Day 113 (±3), and Day 141 (±3).<br>Prior to the first infusion of AK002 or placebo, patients will self-administer 60 mg oral prednisone 12–24 hours before the predicted start of infusion. A steroid premedication prior to the start of the second through sixth infusions may only be administered with the written approval of the Medical Monitor.<br>The initial infusion should be given over at least a 4-hour period, and the second infusion should be given over at least a 3-hour period. The third and all subsequent infusions should be given over at least a 2-hour period, depending on the patient's tolerance of the previous infusions and at the Investigator's discretion.<br>Any changes in the infusion rate schedule due to tolerability will not be considered deviations from the protocol, as long as the maximum infusion speed is not exceeded or increased beyond the protocol specified limits.<br>All infusions must be completed within 8 hours of the study drug being mixed with NaCl. |
| **Duration of Subject Participation** | The total study duration for each patient will be approximately 8 months. This includes:<br>• A screening period of 18–45 days prior to study drug administration.<br>• A treatment period of 20 weeks.<br>• A follow-up period of 84 days (±3) following the last dose of study drug.<br>• Patients who enroll in the AK002-016X extension study will participate in the AK002-016 study for 26–32 weeks and will complete the study at least through the Day 176 visit. |

| | |
|---|---|
| **Duration of Subject Participation cont.** | • Patients who enroll in AK002-016X prior to Day 197 will not complete the Day 197 or Day 225 procedures under Protocol AK002-016.<br>• Patients who enroll in AK002-016X after Day 197 but prior to Day 225 will not complete the Day 225 procedures under Protocol AK002-016. |
| **Safety Evaluations** | Safety and tolerability will be assessed throughout the study by monitoring and evaluating AE including any complications resulting from the IV infusion. All TEAE will be collected from the start of study drug administration in AK002-016 through the start of study drug administration in AK002-016X if enrolling in the AK002-016X extension study, Day 225 if not enrolling in the AK002-016X study, or Early Termination (ET).<br><br>Severity will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (or most current version). All AE will be assigned a severity grade and will be assessed for clinical significance and relationship to study drug.<br><br>Additional safety evaluations include clinical laboratory tests, comprising anti-drug antibody (ADA) to AK002, complete blood counts, chemistries and urinalyses, physical exams (PE), and vital signs measurements.<br><br>The Medical Monitor will review blinded safety data throughout the study. Certain safety data (post-treatment cell differentials as well as tissue eosinophil and CCI [redacted]) will not be provided to study sites or to the Sponsor as it may cause bias. The designated Safety Monitor will review blinded safety data as well as post-treatment cell counts and will escalate to the Medical Monitor as needed in a manner that does not cause bias.<br><br>An independent Data Monitoring Committee (iDMC) has been convened and will meet at regularly scheduled intervals in accordance with the iDMC charter. |
| **Efficacy and Pharmacodynamic Evaluations** | Daily self-administration of a disease-specific patient questionnaire, the Eosinophilic Gastritis/Duodenitis PRO will be used to evaluate signs and symptoms associated with EG and/or EoD. Patient TSS will be evaluated, capturing the 6 common symptoms of EG/EoD (abdominal pain, nausea, abdominal cramping, loss of appetite, fullness before finishing a meal [early satiety], and bloating). Vomiting and diarrhea will also be captured but will not be included in the TSS.<br><br>Biopsies of gastric and duodenal mucosa collected during pre-treatment and post-treatment EGD will be evaluated for number of eosinophils. In addition, the CCI [redacted] will be evaluated in patients with CCI [redacted]. The CCI [redacted] will be evaluated prior to each infusion and 1 hour (±15 minutes) after the end of each infusion. |

| | |
|---|---|
| **Efficacy and Pharmacodynamic Evaluations cont.** | For patients with concomitant allergic asthma or atopic dermatitis, evaluation will include a question for each about the severity of symptoms over the past 24 hours. For all patients during the screening period, daily evaluation will include a question about the severity of dysphagia over the past 24 hours. After randomization, this dysphagia question will continue for patients scoring ≥3 on any 2 weeks of screening dysphagia completion.<br><br>Patients will rate their quality of life using the non-disease-specific CCI at various study visits.<br><br>Patients will rate their impression of disease severity CCI and disease improvement CCI at specified time points during the study. |
| **Pharmacokinetic Evaluations** | Blood (serum) will be collected for assessment of AK002 concentrations using a validated enzyme-linked immunosorbent assay (ELISA) method.<br><br>Pharmacokinetic (PK) blood samples will be obtained on Days 1, 8, 15, 29, 57, 85, 113, 141, 169, 176, 197, and 225 or 28, 35, 56, and 84 (±3) days after last dose of study drug, if ET. On dosing days (Days 1, 29, 57, 85, 113, and 141), blood for PK will be collected predose.<br><br>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, as well as on Days 8, 15, 169, 176, 197, and 225 or 28, 35, 56, and 84 (±3) days after last dose of study drug, if ET, and in the event of a suspected immunogenicity-related AE. |
| **Sample Size Calculation** | **First Co-Primary Endpoint:** A sample size of 80 patients per treatment group will have >99% power to demonstrate a greater proportion of responders at Week 24 in AK002 patients when compared to placebo patients, assuming the proportions of responders are 0.6 and 0.1 in AK002 and placebo groups, respectively.<br><br>**Second Co-Primary Endpoint:** A sample size of 80 patients per group will provide 96% power to detect a statistically significant difference of 7.4 points between AK002 and placebo in the mean reduction from baseline in TSS at Weeks 23–24, assuming a common standard deviation of 12.5 points and a population mean Baseline TSS of 30 points (AK002-003 data on file). |
| **Statistical Analysis** | The primary efficacy analysis population is the Modified Intent-to-Treat (MITT) population, defined as all randomized patients who have received at least 1 infusion of study drug. The secondary efficacy analysis population is the Per Protocol (PP) population, defined as MITT patients who have received at least 1 infusion of study drug and did not have significant protocol violations possibly interfering with assessment of efficacy. The safety population is defined as all patients who are randomized and have received at least 1 infusion of study drug. |

| | |
|---|---|
| **Statistical Analysis cont.** | The MITT population will be used for all efficacy analysis. The Per Protocol population will be used for the primary endpoints and select secondary endpoints analyses. The Safety population will be used for all safety analysis.<br><br>Patient disposition and reason for early discontinuation will be tabulated. Patient demographics, baseline characteristics, and treatment exposure will be summarized.<br><br>**Efficacy Analysis:** To evaluate the clinical benefit of AK002 in adult patients with active EG and/or EoD when compared with placebo, efficacy endpoints will be co-primary.<br><br>The first co-primary endpoint will be analyzed using the Fisher's exact test comparing AK002 with placebo for the proportion of treatment responders. Patients who experience an intercurrent event (i.e., exit the study prematurely or initiate prohibited or restricted medications) prior to the end of Week 24 will be treated as non-responders. Proportion of responders and the associated 95% confidence interval (CI) will be presented for each treatment group. Additionally, the between group difference and the associated 95% CI will be computed and presented.<br><br>Sensitivity analysis will be carried out using the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors (Baseline TSS<28 vs ≥28 and EG ± EoD [i.e., EG with or without EoD] versus EoD-only).<br><br>The second co-primary endpoint will be analyzed by analysis of covariance (ANCOVA). The least square (LS) mean, standard error (SE), and 95% Confidence Interval for each treatment group and for the between group difference will be derived from ANCOVA with treatment as a factor, Baseline PRO TSS (continuous) and EoD without EG (categorical) as covariates. Data on patients who experience an intercurrent event (i.e., exit the study prematurely or initiate prohibited or restricted medications) prior to the end of Week 24 will be set to missing.<br><br>Detailed specifications for the missing data imputation will be provided in the Statistical Analysis Plan (SAP).<br><br>Analysis of binary secondary endpoints will be based on the methods outlined above for the first co-primary efficacy analysis.<br><br>Change from baseline in continuous secondary outcomes measured at multiple post-baseline time points will be analyzed longitudinally using a mixed model. The model will include fixed effects for baseline value, treatment, week, and the treatment by week interaction and allow for random subject effects and assume an unstructured covariance structure. 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. Least square means and the 95% CI for the between group difference will be estimated for each week. |

| | |
|---|---|
| **Statistical Analysis cont.** | Another analysis to use is the same mixed model for repeated measures (MMRM) model but with missing weekly TSS scores imputed under the missing not at random (MNAR) assumption. This imputation assumes the AK002 patient response follows the placebo patient response trajectory.<br><br>Empirical cumulative distribution function (eCDF) and probability distribution function (PDF) of the change from baseline in TSS will be plotted by treatment group to demonstrate consistency of the treatment effect.<br><br>To control for the overall false-positive error rate, the hypothesis testing for the primary and secondary endpoints using the MITT population are ordered as follows:<br><br>• The 2 co-primary efficacy endpoints will each be tested 2-sided at $\alpha$=0.05 level.<br><br>• If both tests are statistically significant, the hypothesis tests for the secondary endpoints will proceed sequentially based on the order specified in the SAP.<br><br>If at any point, the statistical test is not significant at 2-sided $\alpha$=0.05 level, the hypothesis testing procedure will stop. All endpoints prior to this point will be considered statistically significant and inferential statistics after this point will be considered descriptive. |

# 2. Background

## 2.1 Siglec-8 and AK002

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

## 2.2 Overview of Nonclinical Studies

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

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

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

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

To evaluate the in vivo activity of anti-Siglec-8 antibodies in an immunocompetent rodent model, a transgenic mouse strain has been developed that selectively expresses human Siglec-8 on the surface of mouse mast cells, eosinophils and basophils. In single- 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 the humans. AK002 showed sustained systemic exposure in Siglec-8 transgenic mice with an extended terminal half-life estimated as 272 hours or 337 hours following single IV administration of 50 mg/kg or 100 mg/kg, respectively. There was no evidence of anti-drug antibodies (ADA) in either study. Decreases in eosinophil counts in both sexes were observed, which reflect the expected pharmacology of AK002. The no-observed-adverse-effect-level (NOAEL) following IV administration of AK002 to transgenic mice was 100 mg/kg, which supports the Phase 1 studies in humans.

### 2.3 Overview of Clinical Studies

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

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

To date, healthy volunteers and patients with ISM, CU, severe AC, EG/EoD, EoE, and mast cell gastritis have been enrolled in clinical studies. In general, AK002 has been well tolerated. The most common treatment-emergent adverse event (TEAE) observed was infusion-related reaction (IRR). Most IRR were mild to moderate and resolved on their own, with no treatment required.

Infusion-related reactions that were serious resolved within approximately 24 hours. Common symptoms of IRR were headache, nausea, sweating, flushing, and redness. Most IRR that occurred during the infusion could be managed by slowing or temporary interruption of the infusion, with minimal intervention. In 6 healthy volunteers who received 2 doses of 0.3 mg/kg, 4 weeks apart, the second dose was better tolerated than the first dose. This is also the case in patients with ISM, CU, AC, and EG/EoD with fewer adverse events (AE) reported during the second and subsequent infusions, when compared to the first infusion.

In all studies there was a transient decrease in lymphocyte count after the AK002 infusion (usually resolving within 1 day) that was not associated with any clinical consequence and a sustained suppression in eosinophils that was consistent with the mechanism of action of AK002. No significant trends were observed for changes in vital signs, electrocardiograms (ECG), clinical laboratory parameters, or physical examinations.

In the randomized, double-blind, placebo-controlled, Phase 2 study of AK002 in 65 patients with EG and/or EoD, patients were randomized to receive monthly doses of placebo, low dose AK002 (0.3, 1, 1, and 1 mg/kg), or high dose AK002 (0.3, 1, 3, and 3 mg/kg) in a 1:1:1 ratio. All primary and secondary endpoints were met in the study. There was a 97% and 92% mean reduction in eosinophils in the stomach/duodenum for the high dose and low dose AK002-treated patients, respectively, versus a 10% increase for placebo-treated patients ($p<0.0001$). The reduction of eosinophils was associated with a statistically significant reduction in total symptom score (TSS) of 58% in the high dose AK002 group and 49% reduction in the low dose AK002 group versus a 24% reduction in the placebo group ($p=0.0012$ and $p=0.015$, respectively). Improvement in symptoms were observed within 24 hours of the first dose of study drug. In addition, 70% of high dose treated patients and 68% of low dose treated patients were treatment responders (defined as >30% improvement in TSS and >75% reduction from baseline in tissue eosinophils) versus 5% for placebo-treated patients ($p<0.0001$).

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

More than 90% of patients in the Phase 2 study elected to continue into a long-term continuation study. In that study, a starting dose of 1 mg/kg was used, followed by subsequent doses of 3 mg/kg. Premedication of 80 mg prednisone was administered the day before the first and

second dose for 20 of the 58 patients dosed. Using this premedication regimen, no IRR were observed on the first infusion of the extension study.

### 2.4 Eosinophilic Gastrointestinal Disorders

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

Eosinophilic gastritis and/or eosinophilic duodenitis (previously referred to as eosinophilic gastroenteritis) represent what are traditionally believed to be rare types of EGID that are characterized by chronic, often severe inflammation due to patchy or diffuse infiltration of eosinophils into layers of the stomach, small intestine, or both the stomach and small intestine (Prussin, 2014; Reed, 2015; Zhang, 2017). The diagnosis is based on clinical presentation (gastrointestinal symptoms) combined with increased tissue eosinophils in biopsy specimens from the stomach and/or duodenum without any other cause for the eosinophilia. Involvement of the small intestine is typically assessed by performing duodenal biopsies using an esophago-gastro-duodenoscopy (EGD) and has been referred to as eosinophilic gastroenteritis or eosinophilic enteritis, though eosinophilic duodenitis (EoD) is more appropriate. The gastrointestinal symptoms are believed to be due to the release of inflammatory mediators from activated eosinophils, and likely mast cells. Symptoms that are often severe and debilitating commonly include abdominal pain, nausea, bloating, early satiety, fullness before finishing a meal, abdominal cramping, vomiting, diarrhea, and weight loss (Alhmoud, 2016; Lopez-Medina, 2015; Mansoor, 2017; Reed, 2015).

Jensen et al. (2016) estimated the prevalence of EG and EoD to be 6.3/100,000 and 8.4/100,000 respectively (for patients ages 1–64 years old). Mansoor et al. (2017) estimated the overall prevalence of EG to be 5.1/100,000 persons.

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

There are no FDA-approved treatments for EG and/or EoD. Current therapies and disease management include dietary restriction/elimination, PPI, antihistamines, systemic or topical corticosteroids, and occasional off-label use of immunomodulatory biologics (Prussin, 2014; Reed, 2015; Zhang, 2017). Proton pump inhibitors have little to no benefit in patients with EG and/or EoD, despite reports of providing partial benefit in some patients with EoE (Katz, 2013). Restricted/elemental diets are not effective long-term treatment as they require strict compliance and, in the case of elemental diets, are expensive and are often not reimbursed by insurance. In

addition, compliance is very poor, and patient quality of life is greatly impacted (Bedell, 2018; Peterson, 2013; Wechsler, 2014). Corticosteroids, systemic or topical (swallowed) have been shown to provide symptom relief but are not appropriate for long-term treatment due to numerous side effects and associated risks including adrenal insufficiency, bone demineralization, increased chance of infection, osteoporosis, behavioral issues, and weight gain.

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

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

## 3. Rationale for Study and Dose Selection

Based on experience with AK002 in healthy volunteers and in patients with ISM, CU, severe AC, and EG/EoD, the proposed AK002 dose regimen of 6 total doses is 1 mg/kg for the first infusion, followed by 5 doses of 3 mg/kg administered every 4 weeks.


CCI [redacted]

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

Subsequent infusions in multiple dose cohorts were associated with fewer IRR when compared with the first infusion. Therefore, the proposed dosing regimen is a starting dose of 1 mg/kg, with a second dose of 3 mg/kg, followed by 4 doses of 3 mg/kg for subsequent infusions for this Phase 3 study with AK002 in patients with EG and/or EoD.

## 4. Study Objectives

### 4.1 Primary Objective

The primary objective of the study is to evaluate the efficacy and safety of AK002 in patients with moderate-to-severe EG and/or EoD when compared with placebo.

Efficacy will be measured by co-primary endpoints, namely:

1) First co-primary endpoint – Proportion of Tissue Eosinophil Responders at Week 24:
   A responder is a patient achieving the following eosinophil counts.
   - EG: Mean eosinophil count ≤4 cells/hpf in 5 highest gastric hpf.
   - EoD: Mean eosinophil count ≤15 cells/hpf in 3 highest duodenal hpf.
   - EG + EoD: Mean eosinophil count ≤4 cells/hpf in 5 highest gastric hpf and mean eosinophil count ≤15 cells/hpf in 3 highest duodenal hpf.
2) Second co-primary endpoint: Change in TSS from Baseline to Weeks 23–24 as measured by the patient reported outcome (PRO) questionnaire.

   The PRO TSS comprises the following 6 symptoms:
   - Abdominal pain intensity
   - Nausea intensity
   - Fullness before meal intensity
   - Loss of appetite intensity
   - Bloating intensity
   - Abdominal cramping intensity

### 4.2 Secondary Objectives

The secondary objectives of the study are to further characterize the efficacy of AK002 as measured by:

- Change in tissue eosinophils from Baseline to Week 24.
- Proportion of patients achieving a mean eosinophil count ≤1 cells/hpf in 5 highest gastric hpf and a mean eosinophil count ≤1 cell/hpf in 3 highest duodenal hpf at Week 24.

- Proportion of treatment responders at Week 24. A responder is defined as >30% improvement in TSS ***and*** mean eosinophil count ≤4 cells/hpf in 5 highest gastric hpf and/or mean eosinophil count ≤15 cells/hpf in 3 highest duodenal hpf.
- Proportion of patients who achieve ≥50% reduction in TSS from Baseline to Weeks 23–24.
- Proportion of patients who achieve ≥70% reduction in TSS from Baseline to Weeks 23–24.
- Change in weekly TSS over time.

### 4.3 Exploratory Objectives

The exploratory objectives are to evaluate the effect of AK002 by comparing AK002 to placebo treatment for the following parameters:

- Change from Baseline in CCI [redacted] over time.
- Change from Baseline in CCI [redacted] over time.
- For patients with CCI [redacted]: Proportion of patients achieving a CCI [redacted] at Week 24.
- Change from Baseline in CCI [redacted] over time.

### 4.4 Safety Objectives

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

### 4.5 Target of Estimation

The estimand (target of estimation) for Protocol AK002-016 is:

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

A key aspect of eligibility is that subjects must complete at least 4 daily PRO questionnaires per week for a minimum of 3 weeks during the screening period. In addition, subjects must have a weekly average score of abdominal pain, nausea, or diarrhea ≥3 on the PRO questionnaire (score from 0–10) for at least 2 weeks of screening and a weekly average TSS of ≥10 for at least 2 weeks of screening

### 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 TSS from Baseline to Weeks 23–24 as measured by the PRO questionnaire.

### 4.5.3 Treatment

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

### 4.5.4 Intercurrent Events

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

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

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

If a prohibited/restricted medication is started during the course of the study, the patient may be withdrawn from study treatment and followed for the 12-week follow-up period. In addition, the follow-up EGD may not be performed. Thus, for the analysis of the study product estimand, tissue eosinophil values and TSS 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 (as detailed in the SAP). 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 Measures

- 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 average of Weeks 23–24 TSS and the between treatment difference in the AK002 and placebo treatment groups LSM.

## 5. Study Design

### 5.1 Study Overview

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

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

Patients will be consented and then screened for 3–5 weeks (18–45 days) prior to Day 1. Patients who meet all eligibility criteria can be enrolled into the study. Patients who do not meet all eligibility criteria at screening or who qualify at screening but are not enrolled may be assigned a new patient identification number and rescreened once. Patients rescreened within 30 days of signing the initial consent will not need to sign a new informed consent form (ICF) providing no changes have been made to the ICF.

The study is designed as follows:

- An 18 to 45-day screening period with baseline evaluations for study eligibility including active symptoms of disease (gathered by the patient reported outcome [PRO] questionnaire completed during screening) and EGD with biopsy.
- Prior EGD may be used for eligibility as long as the EGD occurred within 30 days of the first screening visit for the AK002-016 study and were performed and centrally assessed as

for the AK002-016 study.

- If patients meet histology and symptom eligibility criteria, they will be randomized and stratified by the highest weekly TSS of disease activity recorded during the screening period (<28 or ≥28 strata) and whether the patient is EoD-only. The IRT will assign patients 1:1 to receive AK002 or placebo; 6 doses will be received.
- Pre-study medications and dietary restrictions should remain unchanged throughout the screening period and throughout the study. Systemic or swallowed steroids above 10 mg daily prednisone (or the equivalent thereof) will not be allowed except as an approved premedication prior to infusion, to treat an IRR that occurs during infusion, or the use is due to unforeseen circumstances when it is deemed medically necessary to treat an unrelated medical condition.
- Eligible patients will receive the first dose of placebo or AK002 (1 mg/kg) on Day 1, with premedication of 60 mg oral prednisone 12–24 hours prior to the start of the infusion.
- If the study drug is well tolerated (no stopping rules being met), patients will receive 5 additional doses of placebo or AK002 (3 mg/kg) on Days 29, 57, 85, 113, and 141. With the exception of Day 1, steroid premedication will only be allowed with the written approval of the Medical Monitor.
- Patients will remain at the site for at least 1 hour of observation following the end of the infusion.
- During the Treatment period patients will return to the clinic for study visits as described in the Schedule of Events (Table 1).
- Daily administration of the PRO questionnaire (including any appropriate additional questions) throughout the study and the follow-up period for all patients.
- An EGD with biopsy will be performed on Day 169 (±3) or 28 (±3) days after last dose of study drug if patient terminates early.
- Follow-up will occur for 84 (±3) days after the last dose of study drug unless patients decide to enter the long-term extension study. Follow-up visits for patients opting not to enter the extension study will occur on Day 176 (±3), Day 197 (±3) and Day 225 (±3).
- Patients who satisfactorily complete AK002-016 have the option to receive AK002 in a separate open-label extension study if all eligibility criteria for the extension study are satisfied. Patients who enroll in the AK002-016X extension study may begin the extension study dosing 1 day after completing the Day 176 visit of this protocol.

- Total study duration is approximately 35–37 weeks. For patients entering the AK002-016X extension study, the total study duration may be as short as 28 weeks.
- Patients may enroll in the AK002-016X extension study any time after the Day 176 visit in the main study has occurred. The Day 197 and Day 225 main study visits will occur if the patient does not enroll in the extension study prior to the scheduled date of these visits. A patient enrolling in the AK002-016X study prior to Day 197 will not complete the Day 197 or Day 225 procedures under this protocol. Open-label dosing and follow-up will occur under the AK002-016X extension study.

## 5.2 Schedule of Events

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

## Table 1 Schedule of Assessments

| | Screening (18–45 days) | | Treatment Period (20 weeks) | | | | | | | | Follow-Up Period[30] (12 weeks) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Baseline**[1] | **Prior to Day 1** | **Dose 1 Day 1** | **Day 8** (±2 days) | **Day 15** (±2 days) | **Dose 2 Day 29** (±3 days) | **Dose 3 Day 57** (±3 days) | **Dose 4 Day 85** (±3 days) | **Dose 5 Day 113** (±3 days) | **Dose 6 Day 141** (±3 days) | **Day 169** (±3 days) or 28 days after last dose | **Day 176** (±3 days) or 35 days after last dose if ET[29] | **Day 197** (±3 days) or 56 days after last dose if ET[29] | **Day 225** (±3 days) or 84 days after last dose if ET[29] |
| Informed consent | X | | | | | | | | | | | | | |
| Demographics | X | | X | | | | | | | | | | | |
| Medical History | X | | X | | | | | | | | | | | |
| Prior/Concomitant Medications | X | | X | | | X | X | X | X | X | X | X | X | X |
| Body weight and height[2] | X | | X | | | X | X | X | X | X | | X | X | X |
| Vital Signs[3] | X | | X | | | X | X | X | X | X | | X | X | X |
| 10 or 12-lead ECG[4] | X | | | | | | | | | | | | | |
| Complete Physical Exam[5] | X | | | | | | | | | | | | | |
| Symptom-Directed Physical Exam[6] | | | X | | | X | X | X | X | X | | X | X | X |
| Baseline Diet Assessment[7] | X | | | | | | | | | | | | | |
| Baseline Diet Compliance[8] | | | X | | | X | X | X | X | X | | X | X | X |
| Stool for Ova and Parasite[9] | X | | | | | | | | | | | | | |
| ePRO Activation and Training[10] | X | | | | | | | | | | | | | |
| ePRO Questionnaire (may include Additional Questions)[11] | <----------Complete electronically one time daily ----------> | | | | | | | | | | | | | |
| [redacted] CCI | X | | X | | | X | X | X | X | X | | X | X | |
| CCI [redacted] | <----------Complete electronically on Screening Day 19, Study Day 7, and Study Day 28 ----------> | | | | | | | | | | | | | |
| CCI [redacted] | <----------Complete electronically on Study Day 7 and Study Day 28----------> | | | | | | | | | | | | | |
| EGD with Biopsy[12,14] | X | | | | | | | | | | X | | | |
| Blood for Screening Chemistry (includes hCG and FSH)[12,15] | X | | | | | | | | | | | | | |

**Table 1 Schedule of Assessments cont.**

| | **Screening** (18–45 days) | | **Treatment Period** (20 weeks) | | | | | | | | **Follow-Up Period**[30] (12 weeks) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Baseline**[1] | **Prior to Day 1** | **Dose 1 Day 1** | **Day 8** (±2 days) | **Day 15** (±2 days) | **Dose 2 Day 29** (±3 days) | **Dose 3 Day 57** (±3 days) | **Dose 4 Day 85** (±3 days) | **Dose 5 Day 113** (±3 days) | **Dose 6 Day 141** (±3 days) | **Day 169** (±3 days) or 28 days after last dose | **Day 176** (±3 days) or 35 days after last dose if ET[29] | **Day 197** (±3 days) or 56 days after last dose if ET[29] | **Day 225** (±3 days) or 84 days after last dose if ET[29] |
| Blood for Serology and *Strongyloides stercoralis* [12,16] | X | | | | | | | | | | | | | |
| Blood for Total Serum IgE[12,17] | X | | | | | | | | | | | X | | |
| Previous Treatments Review | X | | | | | | | | | | | | | |
| Eligibility Assessment | X | X | X | | | | | | | | | | | |
| Access IRT: Stratification and Randomization[18] | | | X | | | | | | | | | | | |
| Access IRT: IP Kit Assignment | | | X | | | X | X | X | X | X | | | | |
| Premedication: Prednisone[19] | | X | | | | | | | | | | | | |
| Study Drug Administration[20] | | | X | | | X | X | X | X | X | | | | |
| Blood for CBC with differential[12,21] | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood for Chemistry[12,22] | | | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood for PK[12,23] | X | | | X | X | X | X | X | X | X | X | X | X | X |
| Blood for ADA[12,24] | X | | | X | X | X | X | X | X | X | X | X | X | X |
| Urine for Urinalysis[12,25] | X | | X | | | X | X | X | X | X | | X | X | |
| Dipstick Pregnancy Test[26] | | | X | | | X | X | X | X | X | | X | X | |
| Non-serious Adverse Events[27] | | | X | | | X | X | X | X | X | X | X | X | X |
| Serious Adverse Events[28] | | | X | | | X | X | X | X | X | X | X | X | X |
| Begin AK002-016X extension study at least 1 day after Day 176 Visit (if applicable)[31] | | | | | | | | | | | | X[33] | X[33] | X[33] |
| Blood for histamine/tryptase[32] | | | X | | | X | X | X | X | X | | | | |

**Table 1 Notes**

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

1) Baseline screening visit can occur over several days within the screening period. Day 1 can begin as soon as eligibility criteria are met and at least 4 diary entries have been completed during the third week of screening.

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

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

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

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

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

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

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

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

10) Activate PRO questionnaire and provide patient with unique username and password. PRO questionnaire should be activated for all patients on screening Day 1. Patients with concomitant history of asthma or atopic dermatitis will receive an extra question, about each, as appropriate. All patients will receive dysphagia question during screening and will continue to receive the question after enrollment if weekly average dysphagia is ≥3 during any 2 weeks of screening.

11) PRO should be completed around the same time each day. Prior to enrollment, the PRO weekly averages of abdominal pain, nausea, and diarrhea over the screening period will be calculated and used to assess eligibility. Weekly average Total Symptom Score (TSS6) will be calculated for eligibility and stratification. PRO weekly average for dysphagia will also be assessed prior to enrollment to determine if the patient should continue receiving the 1-question daily dysphagia question.

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

**Table 1 Notes cont.**

13) To be completed electronically by patient, in clinic, prior to any blood draw, physical exam, or vital sign measurements.

14) See Appendix 5 for biopsy assessments. The post-treatment endoscopy (EGD) and biopsy assessments will be performed on Day 169 (±3) or 28 (±3) days after last dose of study drug if ET. If the Day 141 infusion occurs out of window, the EGD should occur 28 (±3) days from the date of Day 141. Post-treatment EGD biopsy results will be blinded to the site.

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

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

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

18) Stratification based on TSS of <28 or ≥28 and whether patient is EoD-only will occur. Randomization and stratification will be conducted through the IRT system.

19) Premedication with 60 mg oral prednisone or approved alternative is required 12–24 hours prior to first infusion. Premedication may be administered prior to subsequent infusions at the Investigator's discretion, but only with written Medical Monitor approval.

20) Study drug will be administered as a single peripheral IV infusion over at least 4 hours for Dose 1 and at least 3 hours for Dose 2. Doses 3–6 should occur over at least 2 hours, depending on prior infusion tolerability. Please refer to the Pharmacy Manual.

21) Blood for CBC with differential, including absolute blood eosinophil count, will be obtained just prior to each infusion, 1 hour (±15 minutes) after the end of each infusion as well as during the screening period, and on Days (±3) 8, 15, 169, 176, 197, and 225 or 35, 56, and 84 (±3) days after last dose if ET. All differential blood counts from Day 1 (post-dose) through the end of the patient's participation will be blinded to the Sponsor and the site. An unscheduled CBC may be collected at the request of the Safety Monitor.

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

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

24) Blood for ADA will be collected predose on dosing Days 29, 57, 85, 113, and 141, as well as during screening and on Days 8, 15, 169, 176, 197, and 225 or 28 (±3), 35 (±3), 56 (±3), and 84 (±3) days after last dose of study drug if ET. ADA sample will also be collected any time an immunogenicity-related AE occurs.

25) Urine for standard urinalysis will be obtained predose on dosing Days 1, 29, 57, 85, 113, and 141 as well as during the screening period and on Day 176 and Day 197 or 35 (±3) days and 56 (±3) days after last dose of study drug if ET.

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

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

**Table 1 Notes cont.**

28) The reporting of SAE occurring after signing Informed consent and prior to the first infusion will be limited to those that relate to screening procedures. The capture of all SAE and AE that are not related to screening procedures will begin at the time of first infusion of study drug.

29) Patients who sign the informed consent for the AK002-016X extension study will complete the procedures for Day 176 and may begin open-label dosing in the extension study, if eligible, one day after the completion of Day 176 visit. In this case, patients will not complete the Day 197 or Day 225 procedures under Protocol AK002-016. Open-label dosing and follow-up will occur under the AK002-016X extension study. Patients who choose to enter the AK002-016X extension study after Day 197 but before Day 225 will not complete Day 225 procedures.

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

31) The final hematology assessment for AK002-016 ***must*** be collected ***prior to*** the subject taking prednisone premedication for AK002-016X. Therefore, dosing in AK002-016X must take place at least 1 day after completion of the Day 176 visit for AK002-016. Subjects may start AK002-016X dosing 1 day after completion of the Day 176 Visit.

32) Blood samples for histamine and tryptase to be collected within 1–2 hours of start of symptoms if there is any suspicion of anaphylaxis.

33) For patients who do not start the extension study before Day 197 or Day 225, visit procedures will occur according to the AK002-016 study.

# 6. Criteria for Evaluation

## 6.1 Safety Endpoints

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

- Adverse events (Section 13) include severity, withdrawals due to AE, and other safety parameters
- ADA (Section 11.5.4)
- Blood chemistry (Section 11.5)
- Hematology (Section 11.2.5)
- Urinalysis (Section 11.5.2)
- Physical examination (Section 11.3.2, 11.3.5)
- Changes in vital signs (Section 11.3.7)
- Changes in concomitant medication use due to AE (Section 11.3.1)

## 6.2 Pharmacokinetic Endpoints

- Blood (serum) will be collected for assessment of AK002 concentrations using a validated enzyme-linked immunosorbent assay (ELISA) method.
- Pharmacokinetic (PK) blood samples will be obtained on screening, predose on Days 29, 57, 85, 113, and 141 and additionally on Days 8, 15, 169, 176, 197, and 225 or 28, 35, 56, and 84 (±3) days after last dose, if ET.
- Blood (serum) will be collected for assessment of ADA using a validated assay method. ADA blood samples will be obtained on screening, predose on Days 29, 57, 85, 113, and 141 and additionally on Days 8, 15, 169, 176, 197, and 225 or 28, 35, 56, and 84 (±3) days after last dose, if ET. AK002 concentrations in serum will be used to calculate AK002 exposure.

## 6.3 Efficacy Endpoints

### 6.3.1 Primary Efficacy Endpoints

Efficacy will be evaluated by co-primary endpoints, namely:

1) First co-primary endpoint – Proportion of Tissue Eosinophil Responders at Week 24:
   A responder is a patient achieving the following eosinophil counts:
   - EG: Mean eosinophil count ≤4 cells/hpf in 5 highest gastric hpf.
   - EoD: Mean eosinophil count ≤15 cells/hpf in 3 highest duodenal hpf.
   - EG + EoD: Mean eosinophil count ≤4 cells/hpf in 5 highest gastric hpf and mean eosinophil count ≤15 cells/hpf in 3 highest duodenal hpf.

2) Second co-primary endpoint: Change in TSS from Baseline to Weeks 23–24 as measured by the PRO questionnaire.

   The PRO TSS comprises the following 6 symptoms:
   - Abdominal pain intensity
   - Nausea intensity
   - Fullness before meal intensity
   - Loss of appetite intensity
   - Bloating intensity
   - Abdominal cramping intensity

### 6.3.2 Secondary Efficacy Endpoints

To characterize the efficacy of AK002 in patients with EG and/or EoD:

- Change in tissue eosinophils from Baseline to Week 24.
- Proportion of patients achieving mean eosinophil count ≤1 cell/hpf in 5 highest gastric hpf and/or mean eosinophil count of ≤15 cells/hpf in 3 highest duodenal hpf at Week 24.
- Proportion of treatment responders at Week 24. A responder is defined as >30% improvement in TSS and mean eosinophil count ≤4 cells/hpf in 5 highest gastric hpf and/or mean eosinophil count ≤15 cells/hpf in 3 highest duodenal hpf.
- Proportion of patients who show ≥50% reduction in TSS from Baseline to Weeks 23–24.
- Proportion of patients who show ≥70% reduction in TSS from Baseline to Weeks 23–24.
- Change in weekly TSS over time.

### 6.3.3 Exploratory Efficacy Endpoints

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

- Change from Baseline in CCI over time.
- Change from Baseline in CCI over time.
- For patients with CCI ): Proportion of patients achieving a CCI at Week 24.
- Change from Baseline in CCI over time.

## 7. Patient Selection

### 7.1 Number of Patients

A total of approximately 160 patients will be dosed in the study in which 80 patients will receive AK002 at a dose of 1 mg/kg for the first dose followed by 3 mg/kg for 5 subsequent doses and 80 patients will receive placebo, in a randomized, double-blind manner. The study will aim to enroll approximately 90 patients with EG ± EoD and approximately 70 patients with EoD only.

### 7.2 Study Population

Male and female EG and/or EoD patients, aged ≥18 and ≤80 years who fulfill the eligibility criteria specified below.

### 7.3 Inclusion Criteria

Patients with EG and/ or EoD are eligible for enrollment into the study if all of the following criteria are met:

1) Provide written informed consent.
2) Male or female aged ≥18 and ≤80 years at the time of signing the informed consent for entry.
3) Baseline endoscopic biopsy with >30 eosinophils/hpf in 5 hpf in the stomach and/or >30 eosinophils/hpf in 3 hpf in the duodenum, as determined by central histology assessment of biopsies collected during the screening EGD, without any significant cause for the eosinophilia.

   Prior EGD may be used for eligibility as long as the EGD occurred within 30 days of the first screening visit for the AK002-016 study and was performed and centrally assessed as for the AK002-016 study.
4) Completion of at least 4 daily PRO questionnaires per week for a minimum of 3 weeks during screening.

5) A weekly average score of abdominal pain, nausea, and/or diarrhea ≥3 on the PRO questionnaire (score from 0–10) and a weekly average TSS of ≥10 for at least 2 weeks of screening.

6) Patients with inadequate or loss of response to, or who were intolerant to standard therapies for EG/EoD symptoms which could include PPI, antihistamines, systemic or topical corticosteroids, and/or diet, among others.

7) If patient is on pre-existing dietary restrictions, willingness to maintain dietary restrictions throughout the study.

8) Willing and able to comply with all study procedures and visit schedule including follow-up visits.

9) Female patients must be either post-menopausal for at least 1 year with FSH level >30 mIU/mL at screening or surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months, or if of childbearing potential, have a negative pregnancy test and agree to use dual methods of contraception, or abstain from sexual activity from screening until the end of the study, or for 120 days following the last dose of study drug, whichever is longer.

   Male patients with female partners of childbearing potential must 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 (e.g., missed or late menstrual period) at any time during study participation.

### 7.4 Exclusion Criteria

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

1) Use of systemic or topical corticosteroids exceeding the equivalent of 10 mg/day of prednisone within 4 weeks prior to the screening visit.

2) Change in the dose of corticosteroids (systemic or topical), PPI, leukotrienes, or diet therapy within 4 weeks prior to screening.

3) Treatment with any immunosuppressive or immunomodulatory drugs that may interfere with the study within 12 weeks prior to the screening visit.

4) Prior exposure to AK002 or known hypersensitivity to any constituent of the study drug.

5) Active *Helicobacter pylori* infection, unless treated and confirmed to be negative prior to randomization and histology per repeat EGD and symptoms still qualify for enrollment after treatment.

6) Confirmed history of inflammatory bowel disease, celiac disease, achalasia, or esophageal surgery.

7) History of bleeding disorders and/or esophageal varices considered to be clinically significant by the Investigator.

8) Other significant causes of gastric and/or duodenal eosinophilia or eosinophilic granulomatosis with polyangiitis (EGPA).

9) Confirmed diagnosis of Hypereosinophilic Syndrome (HES).

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

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

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

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

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

15) Positive helminthic infection on Ova and Parasite (O&P) test.

16) Seropositive for *Strongyloides stercoralis* at screening, except for patients with past but resolved disease.

17) Seropositive for HIV or hepatitis at screening, except for vaccinated patients or patients with past but resolved disease.

18) Vaccination with live attenuated vaccines within 30 days prior to initiation of treatment in the study, during the treatment period, or vaccination expected within 5 half-lives (4 months) of study drug administration. All types and formulations of vaccines (including live attenuated vaccines) authorized by FDA or other regulatory authority for the prevention of COVID-19 may be administered before, during, or after this study. The vaccine should not be administered within 7 days prior to and within 7 days after the administration of AK002 so that any side effects caused by either of the 2 medications can be more easily determined.

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

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

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

### 7.5 Safety Evaluations

Safety and tolerability will be assessed throughout the study by monitoring and evaluating AE including any complications resulting from the IV infusion. All TEAE will be collected from the start of study drug administration in AK002-016 through the start of study drug administration in AK002-016X (Day 176 if enrolling in the AK002-016X extension study), Day 225 if not enrolling in the AK002-016X study, or Early Termination (ET).

Severity will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (or most current version). All AE will be assigned a severity grade and will be assessed for clinical significance and relationship to study drug.

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

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

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

## 8. Prior and Concurrent Medications

Prior and concomitant medications include both prescribed and over-the-counter medications and will be recorded in the electronic Case Report Forms (eCRF) for 30 days prior to the screening visit. Prior medications used for the treatment of EG and/or EoD symptoms, even if they are >30 days before the screening visit will be documented in the eCRF.

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

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

## 8.1 Prohibited Medications

Any biologics or other medications that may interfere with the study, such as immunosuppressive or immunomodulatory drugs (i.e., azathioprine, JAK inhibitors, 6-mercaptopurine, methotrexate, cyclosporine, tacrolimus, anti-TNF, anti-IL-5, anti-IL-5 receptor, dupilumab, anti-IgE antibodies, omalizumab) are prohibited medications. 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.

If a prohibited medication other than corticosteroids as described above is started during the course of the study, the patient may be withdrawn from study treatment and followed for the 12-week follow-up period. The follow-up EGD may not be performed.

## 8.2 Allowed Medications

Medications, other than those that are prohibited (Section 8.1) such as antihistamines, leukotriene antagonists, and sodium cromolyn, are allowed during the study and, unless required due to unforeseen medical necessity, doses are to remain stable. All medication use during the screening period and throughout the study will be documented in the CRF. Any medications used for the treatment of IRR are not considered deviations from the protocol.

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.

The use of systemic or topical corticosteroids with a dose of >10 mg/day of prednisone or equivalent is permitted if it is deemed to be medically necessary to treat an unrelated medical condition or when given as a premedication prior to infusion or to treat an IRR that occurs during infusion.

# 9. Study Treatment

## 9.1 Formulation of Test Product and Placebo

AK002 is a humanized non-fucosylated IgG1 monoclonal antibody directed against Siglec-8. AK002 drug product is supplied as a sterile liquid in a single-use 10R glass vial with a fill volume of not less than 10 mL. The product is stored at 2°C to 8°C. The AK002 formulation is CCI [redacted] pH 6.0, in sterile Water for Injection.

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

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

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

## 9.3 Supply of Study Drug to the Investigational Site

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

## 9.4 Study Drug Dosage/Dosage Regimen

Patients will be randomly assigned through the IRT system to an active dose group of 1 mg/kg AK002 followed by 5 doses of 3 mg/kg or placebo. The exact dose will be calculated prior to each infusion and based on current patient weight. Study drug will be administered as a single peripheral 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).

## 9.5 Preparation of Study Drug

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

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

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

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

## 9.6 Study Drug Administration

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

A volume of 100 mL* of the calculated dose of study drug will be infused over at least 4 hours on Study Day 1, over at least 3 hours on Study Day 29 (±3), and over at least 2 hours on Study Days 57 (±3), 85 (±3), 113 (±3), and 141 (±3). If the infusion is slowed or interrupted, the time may be extended longer than 4 hours, as long as it does not exceed 8 hours.

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

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

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

completed within 8 hours of preparation. Administration will also be discontinued in any patient experiencing a SAE during the course of the infusion.

The patient will be observed for at least 1 hour after the end of each infusion, as per Investigator discretion.

### 9.7 Study Drug Storage

Study drug will be stored by the study sites at 2°C to 8ºC under lock at the designated pharmacy location. Access will be restricted to designated pharmacy staff. The 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, it 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 if it can be used.

### 9.8 Study Drug Accountability

The site's study pharmacist/designee is responsible for maintaining accurate and current records accounting for the receipt, dispensing, preparation, use, return (or destruction), and final disposition of all investigational product (IP).

All dosage calculations will be documented on the source documents. The Master IP Accountability Log should be used to capture receipt, dispensing, and return (or destruction). Electronic IP accountability systems may be used, depending on site preference, as long as the same information is captured. The study monitor will verify entries on these documents throughout the course of the study.

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

## 10. Patient Numbering, Stratification, Randomization, and Blinding

### 10.1 Patient Numbering

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

- The first 3 digits designate the study number. For this study, the number is 216.
- The second 3 digits designate the site number.
- The last 3 digits designate the order of consent at the site (the first patient who provides consent is 001, the second patient is 002, etc.).

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

### 10.2 Stratification and Randomization

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

If the patient qualifies for the study after completing all of the screening procedures, on the day prior to or on the day of first infusion (Study Day 1), the site will access the IRT system in order to stratify and randomize the patient in the study and enter the current body weight for study drug dose calculation. The site will enter the highest weekly TSS of disease activity recorded during the screening period in order to stratify patients into screening TSS <28 or ≥28 strata. The site will also enter whether the patient falls into the category of EoD only.

The IRT system will then randomly assign the patient at a 1:1 allocation ratio to AK002 at a dose of 1 mg/kg (first dose) followed by 3 mg/kg for 5 subsequent doses or placebo in a double-blind manner and will send an email to the pharmacist and/or designee detailing the kit number(s) to use to prepare the infusion.

Approximately 80 patients will be randomized to treatment with AK002 at a dose of 1 mg/kg first dose and 3 mg/kg subsequent doses, and approximately 80 patients will be randomized to placebo. This study will aim to enroll approximately 90 patients with EG ± EoD and approximately 70 patients with EoD only.

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

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

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

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

### 10.3 Blinding

The identity of test and control treatments will not be known to Investigators, Sponsor, research staff, patients, or the study monitor.

The following study procedures will be in place to ensure double-blind administration of study treatments:

- Access to the randomization codes will be strictly controlled by the IRT.
- Throughout the study, the blind should remain unbroken except for an emergency when knowledge of the patient's study medication is necessary for further management or if required for regulatory reporting. The Allakos Medical Monitor approves any emergency blind break, if possible, prior to the unblinding.
- The AK002 and placebo for infusion will be identical in appearance.
- Results from the analysis of blood samples for peripheral hematology differential cells will not be provided to the Investigator and Sponsor until after database lock. Real-time safety monitoring of differential cells will occur by the Safety Monitor.
- Results from the analysis of blood samples for PK and ADA will not be provided to the Investigator and Sponsor until after database lock.
- Results from the analysis of blood samples for histamine/tryptase tests will not be provided to the Investigator and Sponsor until after database lock, unless required for immediate safety reasons.

- After the initial infusion of study drug and prior to enrolling in the AK002-016X extension study (if applicable), results of the assessments noted below will not be provided to the Investigator and Sponsor until after database lock so as to not introduce bias. The results will be reviewed on an ongoing basis by the Safety Monitor and escalated as appropriate.
  - Differential cell counts including neutrophils, eosinophils, basophils, monocytes, and lymphocytes.
  - Enumeration of eosinophils and CCI from Day 169 EGD biopsies.

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

### 10.4 Breaking the Blind

Breaking the blind in a clinical trial on an emergency basis by the site should only occur when knowledge of the treatment to which a subject was allocated would have implications for the emergency medical management of the subject or if required for regulatory reporting, or if there is a pregnancy during the pregnancy reporting period. If necessary, emergency breaking of the blind can be conducted through the IRT by registered site users and/or the Medical Monitor. Whenever possible, the Investigator should contact the Medical Monitor before an emergency breaking of the blind. Reason for unblinding, person conducting the unblinding, personnel who know the unblinded treatment, and date/time of unblinding will be recorded.

## 11. Study Procedures and Guidelines

Table 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:

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

## 11.1 Dietary and Lifestyle Restrictions

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

## 11.2 Pharmacodynamic/Efficacy-Related Procedures

### 11.2.1 EG/EoD PRO Questionnaire

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

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

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

If patients have a history of concomitant atopic dermatitis or asthma, an extra question will be populated for each relevant condition on the ePRO website for the patient to complete daily. All patients will receive an extra question about dysphagia during screening, and patients with a weekly average >3 on at least 2 weeks during screening will continue receiving this question after enrollment into the study. A paper version of these questions (Appendix 10) is available, should the website not be accessible, or the patient not have internet access.

### 11.2.2 CCI [redacted]

An electronic version of the CCI [redacted] (Appendix 2) will be completed by the patient at the screening visit, predose on infusion Days 1, 29, 57, 85, 113, and 141 and on follow-up Day 176 and Day 197 or 35 (± 3) days and 56 (±) 3 days after last dose of study drug if ET. A paper version of this questionnaire will also be available for completion in case the electronic questionnaire is not available to the patient. This information will be entered into the EDC by the study site.

### 11.2.3 CCI [redacted]

An electronic version of the CCI [redacted] (Appendix 9) will be completed by the patient on Study Day 7 and Day 28. An electronic version of the CCI [redacted]

CCI (Appendix 8) will be completed by the patient on Screening Day 18 as well as on Study Day 7 and Day 28. A paper version of these questionnaires will also be available for completion in case the electronic questionnaire is not available to the patient. This information will be entered into the EDC by the study site.

### 11.2.4 Esophago-Gastro-Duodenoscopy with Biopsy

An EGD with biopsy will be performed during the screening period and on Day 169 (±3 days) or 28 (±3) days after the last dose of study drug if ET. If the last infusion on Day 141 occurs outside the protocol-specified window, the EGD date should be moved so that it occurs 28 (±3) days from the date of the last dose, even if this does not fall on Day 169 (±3 days). Biopsy samples will be collected according to standardized instructions and will be sent to the central laboratory (or designee) for fixing and staining. A blinded central reader will report, among other things, maximum number of eosinophils per hpf and maximum number of tryptase-positive mast cells per hpf, and gastric biopsies will be graded using the Sydney System on inflammation, metaplasia, atrophy, and reactive gastropathy. The Marsh Scale Classification will be used to grade duodenal samples.

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

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

- Inclusion Criterion #3: Baseline endoscopic biopsy with ≥30 eosinophils/hpf in 5 hpf in the stomach and/or ≥30 eosinophils/hpf in 3 hpf in the duodenum.
- Exclusion Criterion #5: Active *Helicobacter pylori* infection, unless treated and confirmed to be negative prior to randomization and histology per repeat EGD and symptoms still qualify for enrollment after treatment.

  ***Note*:** A diagnosis of active *H. pylori* at screening may be treated with standard therapies and a repeat EGD completed prior to enrollment to verify that histology criteria are still met and symptoms remain consistent. If *H. pylori* is still present on repeat EGD but UBT and other clinical assessments of active infection are negative, the patient may be randomized into the study.

### 11.2.5 Complete Blood Count with Differential

Blood will be obtained for complete blood count (CBC) with differential at the screening visit, as well as predose and 1 hour (±15 minutes) postdose on Days 1, 29, 57, 85, 113, and 141 and on Days 8, 15, 169, 176, 197, and 225 or 28, 35, 56, and 84 (±3) days after last dose of study drug if ET. The blood sample will be processed and shipped in accordance with laboratory manual and lab kit instructions. A central laboratory will analyze the blood sample and provide results for CBC with differential including hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell count, and absolute differential count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils).

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

### 11.2.6 Baseline Diet Assessment

During the screening visit the Investigator or designee will ask the patient a standardized series of dietary assessment questions (Appendix 3). This baseline diet assessment involves questions regarding food behavior and patterns, as well as types of foods generally avoided, and will serve to establish the baseline diet. Answers will be documented in the source documents and recorded in the eCRF. This baseline diet should be maintained, as much as possible, throughout the course of the study, even if symptoms improve. Compliance with the baseline diet will be assessed at study visits on Days 1, 29, 57, 85, 113, 141, 176, 197, and 225 or 35, 56, and 84 (±3) days past last dose of study drug if ET. Whether or not the patient has maintained the baseline diet and what deviations were made, if applicable, should be documented in the source documents and the eCRF.

### 11.2.7 Previous Treatments Review

During the screening visit the Investigator or designee will ask the patient about the various treatments or methods of symptom control that they have tried in relation to their EG/EoD symptoms. These may be under the supervision of a doctor or self-attempted by the patient. These may include medications (prescription or OTC), food type/eating avoidance or adaptive behaviors, as well as alternative medicine (i.e., acupuncture or hypnotic therapy).

## 11.3 Safety-Related Procedures

### 11.3.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at screening and at study visits if changes are made. Dose, route, unit, frequency of administration, indication for administration, and dates of medication will be captured. Any prior medication received within 30 days before screening and during the study through Day 225 (±3) or 84 (±3) days after last dose of study drug, if ET, will be recorded, or through the first dose of study drug in AK002-016X if patient enters the AK002-016X extension study.

### 11.3.2 Complete Physical Examination

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

### 11.3.3 Body Weight and Height

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

### 11.3.4 Stool Sample for Ova and Parasite

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

A sample collected and analyzed by the central laboratory within 30 days prior to screening may be used to satisfy eligibility for the AK002-016 study and a duplicate sample will not be collected.

### 11.3.5 Symptom-Directed Physical Examination

A symptom-directed physical exam, an examination of reported or observed subject symptoms warranting examination (in the opinion of the Investigator), including assessments of possible infusion site reactions and IRR, will be performed by either the Investigator or a qualified designee at all study visits during the treatment period and follow-up period. New, abnormal physical exam findings must be documented and will be followed by the Investigator or Subinvestigator at the next scheduled visit or sooner if clinically indicated or referred to a non-study Physician.

### 11.3.6 Electrocardiogram

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

### 11.3.7 Vital Signs

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

On dosing days, vital signs will be measured within 30 minutes predose, 15 (±5) minutes after the start of infusion, immediately following the end of infusion (+15 minutes), and just prior to discharge. Please refer to the schedule of events in Table 1.

## 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 planning treatment administration 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.

Clinical laboratory testing may be performed locally if the site thinks the central laboratory may not be able to provide results in a timely fashion due to staff reductions, shipping issues, or other factors associated with the COVID-19 pandemic. The site will strive to use the central laboratory whenever possible.

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

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

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

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

- Repeat the test to verify the out-of-range value.
- Follow the out-of-range value to a satisfactory clinical resolution.
- Record as an AE any laboratory test value after start of study drug that:
  - The Investigator considers clinically significant
  - Requires a patient to be discontinued from the study
  - Requires a patient to receive treatment

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

### 11.5 Blood Chemistry Profile

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

### 11.5.1 Pregnancy Test and Follicle-Stimulating Hormone

A serum pregnancy (hCG) test will be completed for all patients of childbearing potential. Women who are surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months or those who are postmenopausal for at least 1 year with FSH level >30 mIU/mL are not considered to be of childbearing potential. At screening, FSH levels will be tested for female patients to confirm post-menopausal vs. childbearing status. Both FSH and hCG samples will be processed by the central laboratory.

Patients with FSH levels ≤30 mIU/mL are considered to be of childbearing potential. For patients of childbearing potential, the site will perform a urine dipstick pregnancy test prior to each study drug dosing and at Day 176 and Day 197 (±3) or 35 and 56 (±3) days after last dose of study drug if ET. This test is to be assessed by the study staff prior to the start of each study drug infusion. If a patient has a positive pregnancy test, dosing will immediately be discontinued.

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

### 11.5.2 Urinalysis

Urine will be obtained for urinalysis at screening and on Days 1, 29, 57, 85, 113, 141, 176, and 197 or 35 and 56 (±3) days after last dose of study drug if ET. The urine sample will be processed and shipped in accordance with the laboratory manual and laboratory kit instructions. A central laboratory will analyze the urine sample for specific gravity, pH, protein, glucose, ketones, blood, and leukocyte esterase.

### 11.5.3 Serology

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

### 11.5.4 Anti-AK002 Antibodies

Blood will be collected for determination of ADA at screening, on Days 8, 15, 29, 57, 85, 113, and 141, and on Days 169, 176, 197, and 225 or 28, 35, 56, and 84 (±3) days after last dose of study drug if ET. An unscheduled blood sample for ADA may also be obtained if a related AE suspected of being associated with immunogenicity occurs. The serum sample will be collected predose and processed and shipped in accordance with the laboratory manual and lab kit instructions. A central laboratory will analyze the sample for anti-AK002 antibodies using a validated assay method.

### 11.5.5 Blood for Pharmacokinetics and Storage

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

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

### 11.5.6 Blood for Histamine and Tryptase

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

### 11.5.7 Blood for IgE

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

### 11.5.8 Blood for *Strongyloides stercoralis*

Blood collected for the screening serology sample will be tested for *Strongyloides stercoralis*. The sample will be processed by the central laboratory. A negative result must be available prior to the first dose of study drug. A positive result could indicate past/resolved infection, and a patient may be enrolled into the study with a positive *Strongyloides stercoralis* results as long as their ova and parasite test is negative for current infection and the Investigator has no clinical indication to believe active infection is present.

### 11.5.9 COVID-19 Testing

Testing for COVID-19 is not required for this study but may be implemented by the study site at any time during the study due to safety regulations or procedures. Testing for COVID-19 may be individually mandated by EGD facilities, and if required, it will be consented through the site and not listed in the AK002-016 informed consent form.

### 11.5.10 Concurrent Screening between AK002-014 and AK002-016

Since the 2 disease indications (EoE and EG/EoD) being studied often have similar and overlapping symptoms, it is acceptable to screen patients at the same time for both studies in order to minimize patient burden and overall amount of time in screening.

If a patient is screened concurrently for both studies, the majority of screening procedures will only be completed once, and not duplicated for both studies. Separate ICF and daily diary entries are required for each study. Only 1 EGD with biopsy will be required and used for evaluation of histological eligibility for each study.

### 11.5.11 Screening Procedures in AK002-014 Used for AK002-016 Eligibility

Since the 2 disease indications (EoE and EG/EoD) being studied often have similar and overlapping symptoms, it is likely that some patients will screen-fail the AK002-014 study due to having histological findings for EG ± EoD. To minimize patient burden and overall amount of time in screening, the following will be implemented for this group of patients:

- Patients that have completed the EG/EoD ePRO Questionnaire in the AK002-014 study screening may use the diary entries that were made for AK002-014 to satisfy inclusion criteria for symptoms. The EG/EoD PRO Questionnaire is identical for both studies. This negates the requirement for 18 days of screening in the AK002-016 study.
- Patients that have blood work (including serology and *strongyloides stercoralis*) and urinalysis completed during AK002-014 study screening may use the laboratory results from those tests instead of repeating the tests for AK002-016 screening.
- Patients that have stool sample testing completed during AK002-014 study screening may use the laboratory results from those tests instead of repeating the same tests for AK002-016 study screening.
- Patients that have an ECG and physical examination completed during AK002-014 study screening may use those findings instead of repeating them for AK002-016 study screening.
- Predose vital signs, predose blood draw, and urine pregnancy test (if applicable) must still be completed for the AK002-016 study.

- An EGD with biopsy does not need to be completed for AK002-016 screening in accordance with Inclusion Criterion 3: "Prior EGD may be used for eligibility as long as the EGD occurred within 30 days of the first screening visit for the AK002-016 study and was performed and centrally assessed as for the AK002-016 study."

Any testing required for the AK002-016 study and not completed during the AK002-014 study screening must be completed prior to enrollment in the AK002-016 study.

The AK002-016 CCI [redacted] should be completed by the patient predose on Day 1.

Stool testing should be repeated for the AK002-016 study in the event of clinical suspicion of helminthic/parasitic infection or if the patient has traveled to areas where parasitic infections are endemic since the AK002-014 stool testing was done.

## 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 infusion.
- Procedures for screening may be performed over the course of multiple visits prior to the first infusion.

### 12.1 Screening Period

1) Obtain written informed consent.
2) Assign the participant a PID.
3) Begin the collection of SAE related to any screening activities.
4) Collect demographics and medical history.
5) Record prior and concomitant medications.
6) Determine body weight and height.
7) Activate patient access to ePRO questionnaire portal and instruct patient on use of the website to complete the questionnaire(s). Use the ePRO Teaching Tool to instruct the patient on use of the electronic platform (Appendix 7).
8) CCI [redacted] to be completed by the patient.

9) Perform baseline diet assessment.

10) Complete previous treatments review.

11) Obtain vital signs before blood draws and after patient at rest ≥5 minutes.

12) Perform a complete physical examination.

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

14) Collect the following samples for the central laboratory:

    a) CBC with differential

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

    c) Urinalysis

    d) Blood for serology testing (includes Strongyloides stercoralis)

    e) Blood for PK

    f) Blood for ADA

    g) Blood for total serum IgE

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

16) Perform a screening EGD with biopsy following procedures provided by Allakos any time during the screening period.

17) CCI to be self-completed by patient on screening Day 18 (not a clinic visit).

18) Using results from the Central Histology Reader, confirm the eosinophil count from the gastric and/or duodenal biopsies qualify the patient for the study and no exclusionary criteria are found on the EGD.

### 12.2 Prior to Day 1

The following procedures will be performed prior to Day 1:

- Patient should self-administer 60 mg oral prednisone (or alternative premedication approved by the Medical Monitor) 12–24 hours prior to infusion start. Patient should remember what time they took the premedication.

### 12.3 Day 1 – Randomization/Infusion 1

1) Prior to the infusion:
   a) Assess the patient for SAEs related to screening procedures.
   b) Confirm continuing eligibility.
   c) Document any changes to health status.
   d) Document any changes to concomitant medications.
   e) Document any changes to baseline diet.
   f) CCI [redacted].
   g) Confirm CCI [redacted] was completed electronically on screening Day 18. If it was not completed have patient complete a paper version of the questionnaire.
   h) Determine body weight.
   i) Urine for urinalysis.
   j) Perform urine pregnancy test (if patient is of childbearing potential).
   k) Collect vital signs within 30 minutes of the start of the infusion.
   l) Perform symptom-directed physical exam, if needed.
   m) Blood for CBC with differential.
   n) Blood for Chemistry.

2) Prior to randomizing the patient in the IRT system, the site will identify the highest weekly TSS of disease activity recorded during the screening period in order to stratify patients to TSS ≥28 or TSS <28 and whether the patient has an EoD-only diagnosis, as identified by the screening EGD. The study coordinator or designee will enter the highest weekly TSS into the IRT on Study Day 1 to stratify the patient, as well as body weight and PID to assign kit(s).

3) The IRT system will then randomly assign the patient to AK002 at a dose of 1 mg/kg (first dose) or placebo in a double-blind manner and will send an email to the pharmacist and/or designee detailing the kit number(s) to use to prepare the infusion, the dose to prepare (1 mg/kg), and the patient's body weight.

4) 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 patient. 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.

5) Infusion of Study Drug:
   a) Infuse 100 mL of study drug over at least 4 hours using an infusion pump. See the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.
   b) Collect vital signs 15 (±5) minutes after the start of infusion.
   c) If anaphylaxis is suspected, a sample of blood should be obtained for plasma histamine level and tryptase within 1–2 hours of the onset of symptoms. Also, an unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.
6) Post-infusion:
   a) Collect vital signs within 15 minutes of the end of the infusion.
   b) Collect CBC with differential 1 hour (±15 minutes) after the end of the infusion.
   c) Observe the patient for at least 1 hour after the end of infusion. Collect vital signs just prior to discharge.

### 12.4 Day 7 (not a Clinic Visit)

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

### 12.5 Day 8 (±2)

1) CBC with differential
2) Chemistry
3) Blood for ADA
4) Blood for PK

### 12.6 Day 15 (±2)

1) CBC with differential
2) Chemistry
3) Blood for ADA
4) Blood for PK

### 12.7 Day 28 (not a Clinic Visit)

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

### 12.8 Day 29 (±3) – Infusion 2

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

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

### 12.9 Day 57 (±3) – Infusion 3

1) Prior to the infusion:

a) Assess the patient for AE and SAE.

b) Document any changes to concomitant medications.

c) Assess baseline diet compliance.

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

e) CCI [redacted]

f) Determine body weight.

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

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

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

j) CBC with differential

k) Chemistry

l) Urinalysis

m) Blood for PK

n) Blood for ADA

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

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

4) Infusion of Study Drug:

a) Infuse 100 mL of study drug over at least 2 hours using an infusion pump. See the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.

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

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

5) Post-infusion:

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

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

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

### 12.10 Day 85 (±3) – Infusion 4

1) Prior to the infusion:

   a) Assess the patient for AE and SAE.

   b) Document any changes to concomitant medications.

   c) Assess baseline diet compliance.

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

   e) CCI .

   f) Determine body weight.

   g) Urinalysis

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

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

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

   k) CBC with differential

   l) Chemistry

   m) Blood for PK

   n) Blood for ADA

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

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

4) Infusion of Study Drug:

   a) Infuse 100 mL of study drug over at least 2 hours using an infusion pump. See the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.

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

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

5) Post-infusion:

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

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

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

### 12.11 Day 113 (±3) – Infusion 5

1) Prior to the infusion:

a) Assess the patient for AE and SAE.

b) Document any changes to concomitant medications.

c) Assess baseline diet compliance.

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

e) CCI [redacted].

f) Determine body weight.

g) Urinalysis

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

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

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

k) CBC with differential

l) Chemistry

m) Blood for PK

n) Blood for ADA

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

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

4) Infusion of Study Drug:

   a) Infuse 100 mL of study drug over at least 2 hours using an infusion pump. See the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.

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

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

5) Post-infusion:

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

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

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

### 12.12 Day 141 (±3) – Infusion 6

1) Prior to the infusion:

   a) Assess the patient for AE and SAE.

   b) Document any changes to concomitant medications.

   c) Assess baseline diet compliance.

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

   e) CCI [redacted].

   f) Determine body weight.

   g) Urinalysis

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

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

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

   k) CBC with differential

   l) Chemistry

   m) Blood for PK

   n) Blood for ADA

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

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

4) Infusion of Study Drug:

   a) Infuse 100 mL of study drug over at least 2 hours using an infusion pump. See the Pharmacy Manual for infusion rates. Record the start and stop times of the infusion including any times the infusion is interrupted.

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

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

5) Post-infusion:

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

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

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

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

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

2) Blood Draws:

   a) Blood for CBC with differential

   b) Blood for Chemistry

   c) Blood for PK

   d) Blood for ADA

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

4) Perform EGD with biopsy following procedures provided by Allakos and all EGD facility standard operating procedures.

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

**If Day 141 (Infusion 6) occurs outside the protocol window:** Do not conduct EGD on Day 169 but rather on a day that is 28 (±3) days after the Day 141 infusion.

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

1) Assess the patient for AE and SAE.
2) Document any changes to concomitant medications.
3) Assess baseline diet compliance.
4) Assess daily diary compliance (including any additional questions).
5) CCI .
6) Determine body weight.
7) Collect vital signs.
8) Perform symptom-directed physical exam, as needed.
9) Blood Draws:
   a) Blood for CBC with differential
   b) Blood for Chemistry
   c) Blood for PK
   d) Blood for ADA
   e) Blood for IgE
10) Urinalysis and urine pregnancy test (if patient is of childbearing potential)
11) Patients who enroll in the AK002-016X extension study will begin extension study dosing ***1 day after*** completing the Day 176 procedures for Protocol AK002-016. Patients may sign consent for the AK002-016X study during participation in the AK002-016 study and may receive the premedication for the first AK002-016X dose as soon as all Day 176 procedures have been completed in the main study. If patients cannot start the extension study 1 day after the Day 176 visit, they will continue participation in the main study. If patients cannot start the extension study within 28 days of the Day 176 visit in the main study, the Day 197 visit will occur.

**For Early Termination:** Perform the visit 35 (±3) days after the last dose of study drug or prior to this, if necessary, to ensure compliance with the visit. If patient discontinues the study more than 35 days after the last dose of study drug, perform the visit as soon as possible. If only one ET visit is possible, EGD and Follow-up Visit 1 may occur on the same day. Blood draws should occur prior to EGD medications, if possible.

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

1) Assess the patient for AE and SAE.
2) Document any changes to concomitant medications.
3) Assess baseline diet compliance.
4) CCI .
5) Determine body weight.
6) Collect vital signs.
7) Perform symptom-directed physical exam, as needed.
8) Urinalysis and urine pregnancy test (if patient is of childbearing potential)
9) Blood Draws:
    a) Blood for CBC with differential
    b) Blood for Chemistry
    c) Blood for PK
    d) Blood for ADA
10) Patients opting to enroll in the AK002-016X extension study after the Day 197 visit will begin extension study dosing within 28 days of completing the Day 197 procedures for Protocol AK002-016. If patients cannot start the extension study within 28 days of the Day 197 visit, they will continue participation in the main study. If patients cannot start the extension study within 28 days of the Day 197 visit in the main study, the Day 225 visit will occur

**For Early Termination:** Perform the visit 56 (±3) days after the last dose of study drug or prior to this, if necessary, to ensure compliance with the visit. If patient discontinues the study more than 56 days after the last dose of study drug, perform the visit as soon as possible.

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

1) Assess the patient for AE and SAE.
2) Document any changes to concomitant medications.
3) Assess baseline diet compliance.
4) Determine body weight.
5) Collect vital signs.
6) Perform symptom-directed physical exam, as needed.
7) Blood Draws:
    a) Blood for CBC with differential
    b) Blood for Chemistry
    c) Blood for PK
    d) Blood for ADA

**For Early Termination:** Perform the visit 84 (±3) days after the last dose of study drug or prior to this, if necessary, to ensure compliance with the visit. If patient discontinues the study more than 84 days after the last dose of study drug, perform the visit as soon as possible.

## 13. Adverse Event Reporting and Documentation

### 13.1 Adverse Events

In accordance with 21 Code of Federal Regulation (CFR) 312.32(b) and International Conference on Harmonisation (ICH) Guidance E2A, an adverse event (AE) is any untoward medical occurrence in a clinical investigation of a subject administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is, therefore, any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

Examples of an AE include:

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

The following examples are not considered AE:

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

All AE, whether elicited by questions from study staff, volunteered, or noted on physical examination/laboratory testing, and regardless of causality or severity, will be assessed and recorded in the eCRF beginning after the first administration of study drug and ending on Day 225 (±3) or 84 (±3) days after the last dose if patient is not enrolling in the AK002-016X extension study, or until the first dose on Day 1 of the extension study, if enrolling in AK002-016X, unless otherwise directed by Allakos.

### 13.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an AE that meets 1 of the following criteria:

- Death
- A life-threatening AE that places the subject at risk of death at the time of the event. It does not refer to an event that hypothetically might cause death if it were more severe.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant disability/incapacity.
- A congenital anomaly/birth defect occurring in the offspring of a study subject.
- Other important medical events may also be considered a SAE when, based on appropriate medical judgment, they jeopardize the patient or require intervention to prevent 1 of the outcomes listed above.

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

Serious adverse events will be assessed and recorded beginning after the first administration of study drug and ending on Day 225 (±3) or 84 (±3) days after the last dose if patient is not enrolling in the AK002-016X extension study, or until the start of the first dose on Day 1 of the extension study, if enrolling in AK002-016X, unless otherwise directed by Allakos.

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

### 13.3 Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) for this study include:

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

Adverse Events of Special Interest will be assessed beginning after the first administration of study drug and ending on Day 225 (±3) or 84 (±3) days after last dose if patient is not enrolling in the AK002-016X extension study, or until the start of the first dose on Day 1 of the extension study, if enrolling in AK002-016X. Any new AESI (or new information related to a previously reported AESI) must be recorded in the AE eCRF and designated as an “adverse event of special interest.”

### 13.4 Infusion-Related Reactions

All AE considered by the Investigator ***to be related to the infusion*** of the biological substance and occurring within 24 hours of the start of the study drug infusion should be captured as 1 AE, termed “IRR.” Common symptoms of IRR include but are not limited to:

- Flushing
- Chills
- Back or abdominal pain
- Chest discomfort or tightness
- Dizziness
- Shortness of breath
- Headache
- Hypotension or hypertension
- Nausea
- Vomiting
- Sweating
- Fever
- Urticaria
- Pruritus
- Bronchospasm

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

Any medications used within 24 hours of an infusion for the treatment of an IRR are not considered prohibited medications.

### 13.5 Anaphylaxis

A suspicion of anaphylaxis will be carefully monitored and treated according to standard of care. Emergency crash cart equipment and medications, including multiple doses of epinephrine, vasopressors, and bronchodilators, will be available at all times during the conduct of the study. To define anaphylactic reactions in a consistent and objective manner, all AE of suspected anaphylaxis will be evaluated using Sampson's Criteria for Anaphylaxis (Appendix 6).
The assessment of an AE will be done pursuant to definitions set forth by ICH Good Clinical Practice (GCP) guidelines and applicable regulatory requirements.

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

### 13.6 Evaluating Adverse Events and Serious Adverse Events

#### 13.6.1 Establishing Diagnosis

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., dysuria, urinary nitrites should be reported as a urinary tract infection). If the diagnosis is not known, individual signs and symptoms should be assessed and recorded in the

AE eCRF as separate AE. The Investigator (or qualified Subinvestigator) must assign the following AE attributes listed below and is responsible for ensuring this information is recorded in the source documentation.

### 13.6.2 Assessment of Intensity

The Investigator will use their clinical judgment as well as the guidelines laid out in the NCI CTCAE Version 5.0 (or most current version) tables (Table 2 and Appendix 4) 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 v. 5.0: Grade refers to the severity of the AE. The CTCAE displays Grades 1–5 with unique clinical descriptions of severity for each AE based on this general guideline.

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

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

### 13.6.3 Assessment of Causality to Study Drug

The Investigator should use their clinical judgment as well as the guidelines in Table 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 AE eCRF beginning after the first administration of study drug and ending on Day 225 (±3) or 84 (±3) days after last dose if patient is not enrolling in the AK002-016X extension study, or until the start of the first dose on Day 1 of the extension study, if enrolling in AK002-016X, unless otherwise directed by Allakos.

Whenever appropriate, the CTCAE (v. 5.0 or most current version) should be utilized for naming common AE (Appendix 4).

### 13.7.2 Serious Adverse Event Reporting

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

SAE report forms will be provided to the investigational site to assist in collecting, organizing, and reporting SAE, and forms must be completed with as much information as is available and should be submitted to the Sponsor within 24 hours of becoming aware of the event. Serious adverse events must also be recorded on the AE eCRF and designated as “serious.”

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

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

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

The patient's condition will be followed by the Investigator or designated Subinvestigator until resolution of the condition or a return to baseline levels. If additional visits are required, the 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 patient's participation in the study must be followed until any of the following occurs:

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

**Serious adverse events must be reported within 24 hours to:**

**SAE Reporting**

Fax: +1-888-237-7475

Email: SAE@allakos.com

### 13.7.3 Pregnancy Reporting

Pregnancies are captured if they occur in female patients or in the sexual partners of male patients from the time the patient is first exposed to the investigational product through Day 225 (±3) or 84 (±3) days after the last dose if patient is not enrolling in the AK002-016X extension study, or until the start of the first dose on Day 1 of extension study, if enrolling in AK002-016X, unless otherwise directed by Allakos.

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

The Investigator must report any pregnancy to Allakos within 24 hours of becoming aware of it using the provided pregnancy reporting forms. The patient must be immediately discontinued from study drug. An uncomplicated pregnancy will not be considered an AE or SAE, but all pregnancies in patients who received AK002 will be followed through term.

Any congenital abnormalities noted at birth in the offspring of a patient who received AK002 will be reported as an SAE. If the patient received AK002, the outcome of any pregnancy and the presence or absence of any congenital abnormality will be recorded in the source documentation and reported to the Medical Monitor and Sponsor.

### 13.7.4 AESI Reporting

Beginning from the time of first study drug infusion and ending on Day 225 (±3) or 84 (±3) days after last dose if patient is not enrolling in the AK002-016X extension study, or until the start of the first dose on Day 1 of the extension study, if enrolling in AK002-016X, unless otherwise directed by Allakos any new AESI (or new information related to a previously reported AESI) must be recorded in the AE eCRF and designated as an “adverse event of special interest.”

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

### 13.8 Medical Monitoring

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

Allakos Medical Monitor

PPD MD

Phone: 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 patient will be discontinued in the event that:

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

### 13.11 Study Stopping Rules

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

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

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

## 14. Discontinuation and Replacement of Patients

### 14.1 Definition of Study Completion

A patient who completes visits through the Day 225 (±3) visit will be recorded as having completed the study.

A patient who completes visits through the Day 176, 197, or 225 (±3) visit and enrolls in the AK002-016X extension study will be categorized as having completed the AK002-016 study.

### 14.2 Early Discontinuation of Study Drug

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

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

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

All patients who discontinue study drug treatment should be encouraged to continue on study and complete assessments and procedures according to the 12-week follow-up period in Table 1, if possible (including follow-up EGD).

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

## 15. Statistical Methods and General Considerations

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

Unless specified otherwise, baseline will be defined as the last 3 weeks of observation before the first IV infusion of the study drug. All patient data will be listed. When appropriate, summary statistics of number of non-missing values, mean, median, standard deviation, minimum, and maximum will be computed for continuous variables and summary statistics of number and proportion will be computed for categorical variables. Two-sided 95% CI will be provided for the mean and proportion. No formal statistical inferences will be made for safety parameters.

### 15.1 Sample Size

A total of approximately 160 patients will be enrolled.

**First Co-Primary Endpoint:** A sample size of 80 patients per treatment group will have >99% power to demonstrate a greater proportion of responders in AK002 patients than in placebo patients, assuming the proportions of responders are 0.6 and 0.1 in AK002 and placebo groups, respectively.

**Second Co-Primary Endpoint:** A sample size of 80 patients per group will provide 96% power to detect a statistically significant difference between AK002 and placebo in the mean reduction from baseline in TSS score, assuming a mean reduction of 16.1 points on AK002 versus 8.7 points on placebo and a common standard deviation of 12.5 points (AK002-003 data on file). Eighty patients per group will provide 96% power to pick up a difference between placebo and AK002 of 7.4 in TSS with a mean Baseline TSS of 30 and a standard deviation (change from baseline) of 12.5. These assumptions are based on data observed in the Phase 2 AK002-003 study.

### 15.2 Analysis Populations

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

The primary efficacy analysis population is **modified intent-to-treat (MITT) population**, defined as all randomized patients who have received at least 1 infusion of the study drug.

The secondary efficacy analysis population is **per protocol (PP) population**, defined as MITT patients who have received at least 1 infusion of study drug and did not have significant protocol violations possibly interfering with assessment of efficacy. The MITT population will be used for all efficacy analysis. The PP population will be used for the primary endpoints and select secondary endpoints analyses. The Safety population will be used for all safety analysis.

The study statistician along with the study team will review protocol deviations to identify patients to be excluded from the Per Protocol Analysis population.

### 15.3 Patient Disposition

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

### 15.4 Demographic and Baseline Characteristics

The following demographic and baseline variables will be summarized:

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

### 15.5 Study Drug Exposure

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

### 15.6 Efficacy Analysis

#### 15.6.1 Primary Efficacy Endpoint Analysis

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

factors (Baseline TSS [<28 vs ≥28] and disease strata [EG ± EoD vs EoD]) to assess robustness of Fisher's exact test results.

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

The second co-primary endpoint will be analyzed by ANCOVA using the imputed data set outlined in the SAP. The LSM, SE, and 95% CI for each treatment group and for the between group difference will be derived from ANCOVA with treatment as a factor, and Baseline PRO TSS (continuous) and EoD without EG (categorical) as covariates. The hypothesis test for the treatment effect will be carried out by the F-test. The synthesizing method will be used to combine the results from multiple imputations.

Two sensitivity analyses will be conducted to assess the departures from the missing at random (MAR) data assumption. 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 events 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 be based on the tipping point method. In this method, the missing biweekly TSS 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). Detailed specifications for the analyses outlined above will be provided in the SAP.

### 15.6.2 Secondary Efficacy Endpoint Analysis

If both tests of the co-primary endpoints are statistically significant, the hypothesis tests for the secondary endpoints will proceed sequentially in a prespecified order specified in the synopsis. If at any point, the statistical test is not significant at 2-sided $\alpha$=0.05 level, the hypothesis testing procedure will stop.

For patients who provide gastric or duodenal only biopsy, the calculation will be based on the average count of the highest readings from the respective mucosa at baseline and Day 169 (Week 24). For patients who provide both gastric and duodenal biopsies, the calculation will be based on the average count of the highest readings from the Day 169 biopsy that correspond in location (gastric or duodenal) to the location with the highest average count at baseline. The change in tissue eosinophil count from baseline to Day 169 will be analyzed using ANCOVA

with treatment as a factor, and baseline eosinophil counts, Baseline PRO TSS, and disease status as covariates. The LSM, SE, and 95% CI for individual treatment groups, and LSM, SE, 95% CI, and p-value for the between treatment difference will be presented.

Proportion of patients achieving gastric and/or duodenal eosinophil count of ≤1 cell/hpf will be analyzed using Fisher's exact test similar to the analysis for the first co-primary endpoint.

Proportion of treatment responders defined by >30% improvement in TSS ***and*** mean eosinophil count ≤4 cells per hpf in 5 gastric hpf and/or mean eosinophil count ≤15 cells per hpf in 3 duodenal hpf will be analyzed using Fisher's exact test.

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

Change in weekly TSS will be analyzed using the MMRM model. The model will include fixed effects for baseline value, treatment, week, and the treatment by week interaction and allow for random subject effects and assume an unstructured covariance structure. 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 and the 95% CI for the between group difference will be estimated for each week.

The eCDF and PDF plots will be presented for change from Baseline TSS score at Weeks 23–24 stratified by CCI and CCI scores.

### 15.6.3 Exploratory Analysis

Analysis of patients with CCI will be carried out similarly using CCI test. Change from Baseline CCI at Week 25 will be analyzed using the CCI similar to the analysis outlined above.

Change from baseline in the CCI will be summarized by CCI

- CCI
- CCI
- CCI
- CCI
- CCI
- CCI

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

The CCI [redacted] will be summed up to derive the CCI [redacted] They will then be analyzed using the CCI [redacted] with CCI [redacted]

### 15.7 Safety Analysis

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

#### 15.7.1 Treatment Emergent Adverse Events

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

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

### 15.7.2 Anti-Drug Antibodies

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

### 15.7.3 Clinical Laboratory Assessments

Samples will be obtained for the clinical laboratory tests identified in Section 11.4, and laboratory tests to be summarized include chemistry, hematology, urinalysis, and AK002 ADA. Descriptive statistics will be used to summarize laboratory results at baseline, each visit, and the change from baseline for each visit. In addition, shift tables will summarize the laboratory results relative to normal reference ranges at baseline and each post-baseline time point.

### 15.7.4 Vital Signs

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

### 15.7.5 ECG

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

### 15.7.6 Physical Exam

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

### 15.7.7 Concomitant Medications

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

## 15.8 Patient Confidentiality

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

Only the PID, patient initials, and demographics will be recorded in the eCRF. If the patient's name appears on any source document collected (A., hospital discharge summary), it must be removed from the document if the document will be viewed by the Sponsor or a sponsor-contracted study vendor not permitted access to patient-identifying information. All study findings will be stored in electronic databases. The patients will give explicit written permission for representatives of the Sponsor, regulatory authorities, and the IRB to inspect their medical records to verify the information collected. Patients will be informed that all personal information made available for inspection will be kept confidential to the extent permitted by all

applicable state, local, and federal data protection/privacy laws and/or regulations and will not be made publicly available. If the results of the trial are published, the patient's identity will remain confidential.

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

## 16. Data Collection, Retention, and Monitoring

### 16.1 Data Collection Instruments

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

### 16.2 Data Management Procedures

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

All procedures for handling and analysis of data will be conducted using good computing practices meeting Food and Drug Administration (FDA) guidelines for handling and analysis of data for clinical trials.

### 16.3 Data Quality Control and Reporting

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

### 16.4 Database Lock/Disclosure of Randomization Code

There will be 2 database locks for this study:

- A provisional database lock after all patients complete the Day 169 visit to allow for the analysis of safety and efficacy data through Day 169.
- A final database lock after all patients 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 records are entered in the database.
- All AE are coded to the satisfaction of the Chief Medical Officer.
- All medications are coded to the satisfaction of the Chief Medical Officer.
- All data queries have been resolved.
- All decisions have been made regarding all protocol violations and ITT population exclusions.
- Written authorizations to lock the database are obtained from Allakos Clinical Data Management and the Chief Medical Officer.

The randomization code for this study will not be revealed until the previous preconditions are fulfilled and documentation of the 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, 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 its designee will retain a copy of all study records in a limited access storage room for a minimum of 2 years after notification that the investigations have been discontinued and the FDA has been notified, or for 2 years after all marketing applications have been approved. The trial master file will be created during the implementation phase of a study, maintained on an ongoing basis throughout the duration of the project, and collated at the end of the study. The files will contain folders that may include but are not limited to the following subcategories:

- Financial agreements
- Regulatory documents
- Independent Ethics Committee (IEC)/IRB Documents
- Drug Accountability
- Correspondence
- Medical Reports
- Patient Data
- Monitoring Visit Reports
- Sample CRF and CRF Guidelines

### 16.7 Monitoring

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

## 17. Administrative, Ethical, and Regulatory Considerations

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

### 17.1 Protocol Amendments

An amendment must be agreed to in writing by Allakos Inc. and submitted to the health authority as a Clinical Trial Application/Investigational New Drug (IND) amendment. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. Written approval of a protocol amendment is not required prior to implementation of changes to the protocol that eliminate immediate hazard to the patient; however, approval must be obtained as soon as possible thereafter. Each protocol amendment must also be signed by the Investigator.

### 17.2 Independent Ethics Committees/Institutional Review Boards

The protocol and ICF will be reviewed and approved by the IEC/IRB of each participating study site prior to study initiation. A Central IRB may be used if permitted by the participating study site. All SAE, regardless of causality, will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

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

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

### 17.3 Informed Consent Form

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

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

The Investigator or designee will review the study and the ICF with each potential patient. The review will include the nature, scope, procedures, and possible consequences of participation in the study. The consent and review must be in a form understandable to the potential patient. The Investigator or designee and the subject must both sign and date the ICF after review and before the patient can participate in the study. The patient will receive a copy of the signed and dated form, and the original will be retained in the site's study files. The Investigator or designee must

emphasize to the patient that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the patient is otherwise entitled.

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

### 17.4 Publications

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

### 17.5 Clinical Study Registration

This clinical study is registered on the Clinical Trial Registry Website, www.ClinicalTrials.gov as NCT #04322604.

### 17.6 Payment to Patients

All patients may be compensated for participating in this study, in accordance with the payment amounts per study day stated in the patient's signed ICF approved by the IRB. If the patient is discontinued from the study prior to the last study visit, the patient will be compensated for each completed study visit on a pro rata basis, as stated in the patient's ICF. After randomization, patients at participating study sites will be compensated for each completed week of daily questionnaires as long as at least 4 questionnaires per week are completed. Patients may be reimbursed for expenses associated with attending study visits. No additional compensation beyond what is stated in the ICF is permitted.

### 17.7 Investigator Responsibilities

By signing the Investigator Protocol Agreement page, the Investigator agrees to:

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

2) Personally conduct or supervise the study.

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

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

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

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

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

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

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

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

## 18. References

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

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

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

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

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.

Hudson S, Herrmann H, Du J, Cox P, Haddad E, Butler B, et al. Developmental, malignancy-related, and cross-species analysis of eosinophil, mast cell, and basophil siglec-8 expression. J Clin Immunol 2011;31(6):1045-53.

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

Katz P, Gerson L, Vela M. Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. The American Journal of Gastroenterology, 2013;108:308–328.

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

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

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

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

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

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

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

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

## 19. Appendices

## 19.1 Appendix 1: PRO Questionnaire

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

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

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

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Over the past 24 hours, please rate the intensity of your **abdominal (stomach) pain** at its worst. | 0 ☐ NO ABDOMINAL PAIN | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | 5 ☐ | 6 ☐ | 7 ☐ | 8 ☐ | 9 ☐ | 10 ☐ WORST POSSIBLE ABDOMINAL PAIN |
| 2. Over the past 24 hours, please rate the intensity of your **nausea (feeling like you have to throw up)** at its worst. | 0 ☐ NO NAUSEA | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | 5 ☐ | 6 ☐ | 7 ☐ | 8 ☐ | 9 ☐ | 10 ☐ WORST POSSIBLE NAUSEA |
| 3. Over the past 24 hours, please rate the intensity of your **vomiting (throwing up)** at its worst. | 0 ☐ NO VOMITING | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | 5 ☐ | 6 ☐ | 7 ☐ | 8 ☐ | 9 ☐ | 10 ☐ WORST POSSIBLE VOMITING |
| 4. Over the past 24 hours, how many times did you **vomit (throw up)**? | [patient to enter number] | | | | | | | | | | |
| 5. Over the past 24 hours, please rate the intensity of your **fullness before finishing a meal** at its worst. | 0 ☐ NO EARLY FULLNESS BEFORE FINISHING A MEAL | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | 5 ☐ | 6 ☐ | 7 ☐ | 8 ☐ | 9 ☐ | 10 ☐ COMPLETE FULLNESS BEFORE FINISHING A MEAL |
| 6. Over the past 24 hours, please rate the intensity of your **loss of appetite (not feeling hungry)** at its worst. | 0 ☐ NO LOSS OF APPETITE | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | 5 ☐ | 6 ☐ | 7 ☐ | 8 ☐ | 9 ☐ | 10 ☐ COMPLETE LOSS OF APPETITE |
| 7. Over the past 24 hours, please rate the intensity of your **abdominal (stomach) cramping** at its worst. | 0 ☐ NO ABDOMINAL CRAMPING | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | 5 ☐ | 6 ☐ | 7 ☐ | 8 ☐ | 9 ☐ | 10 ☐ WORST POSSIBLE ABDOMINAL CRAMPING |

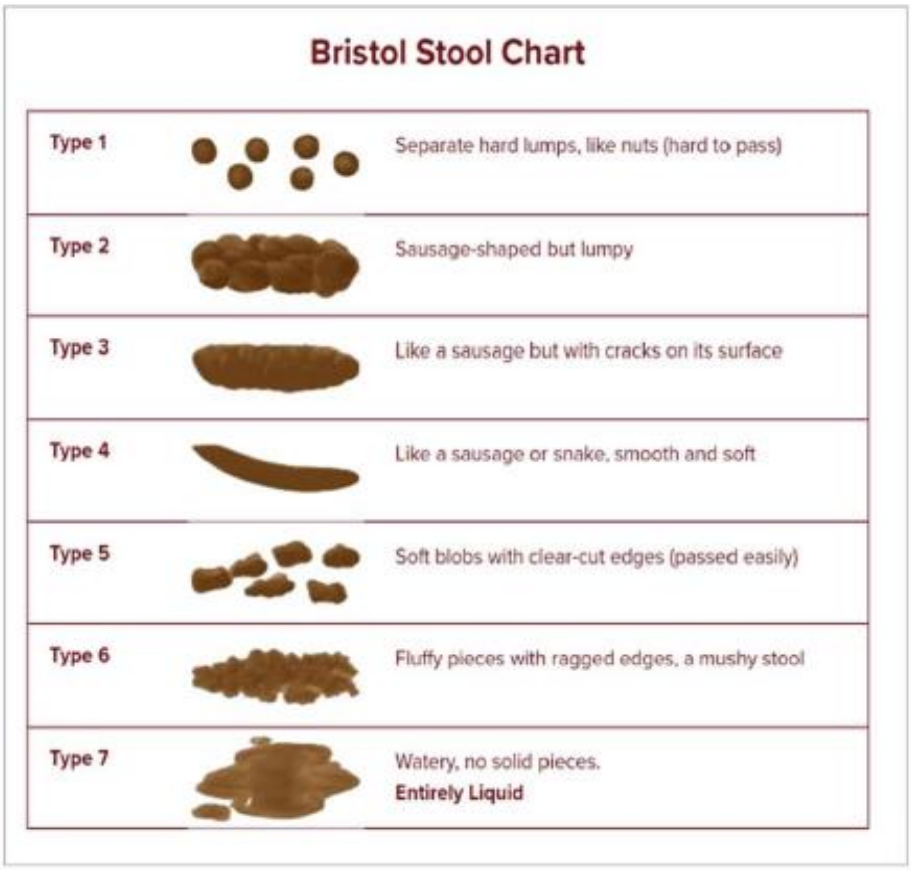
v 29Nov2020 Page 1 of 3

## 19.1 Appendix 1: PRO Questionnaire cont.

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

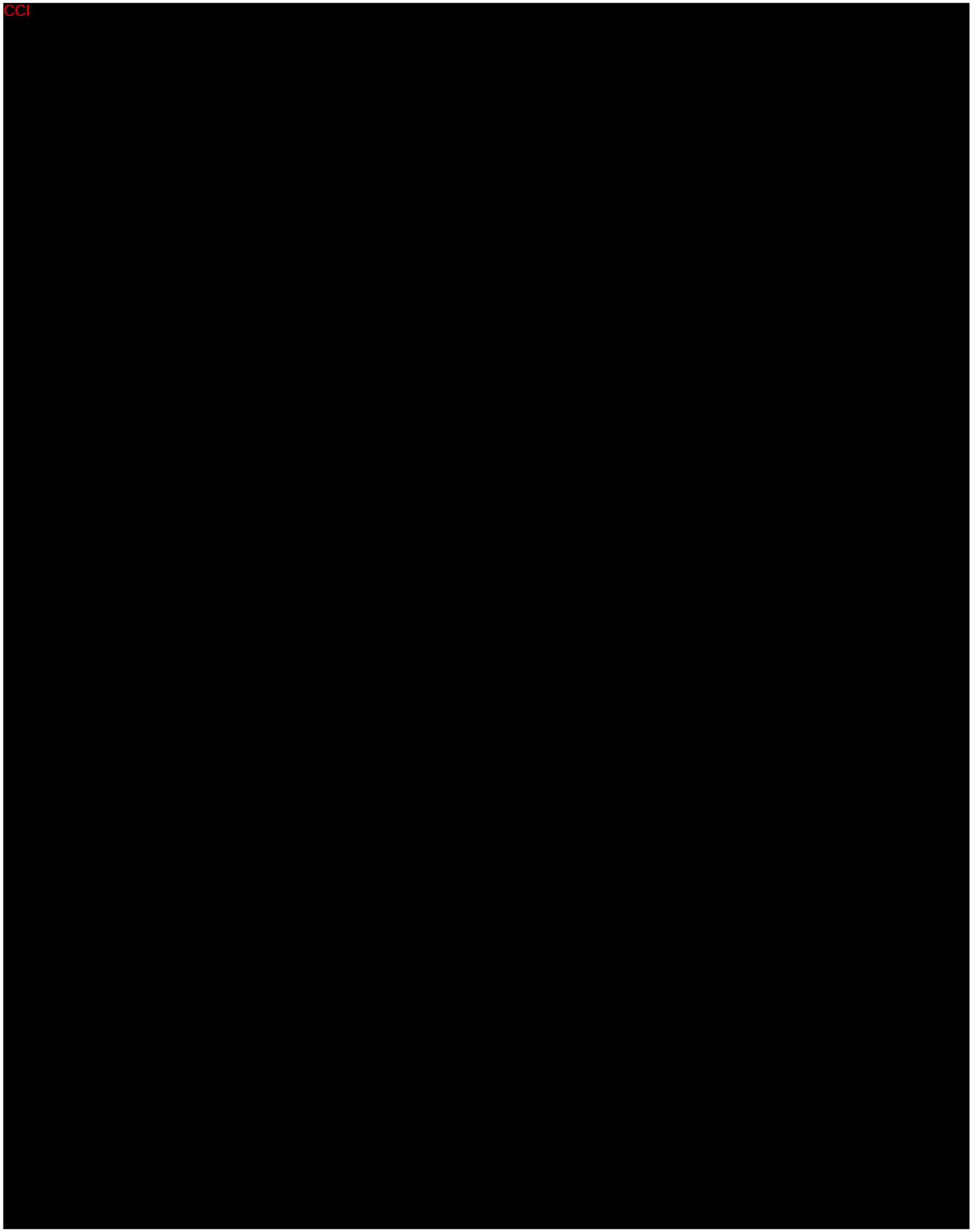
v 29Nov2020 Page 2 of 3

## 19.1 Appendix 1: PRO Questionnaire cont.



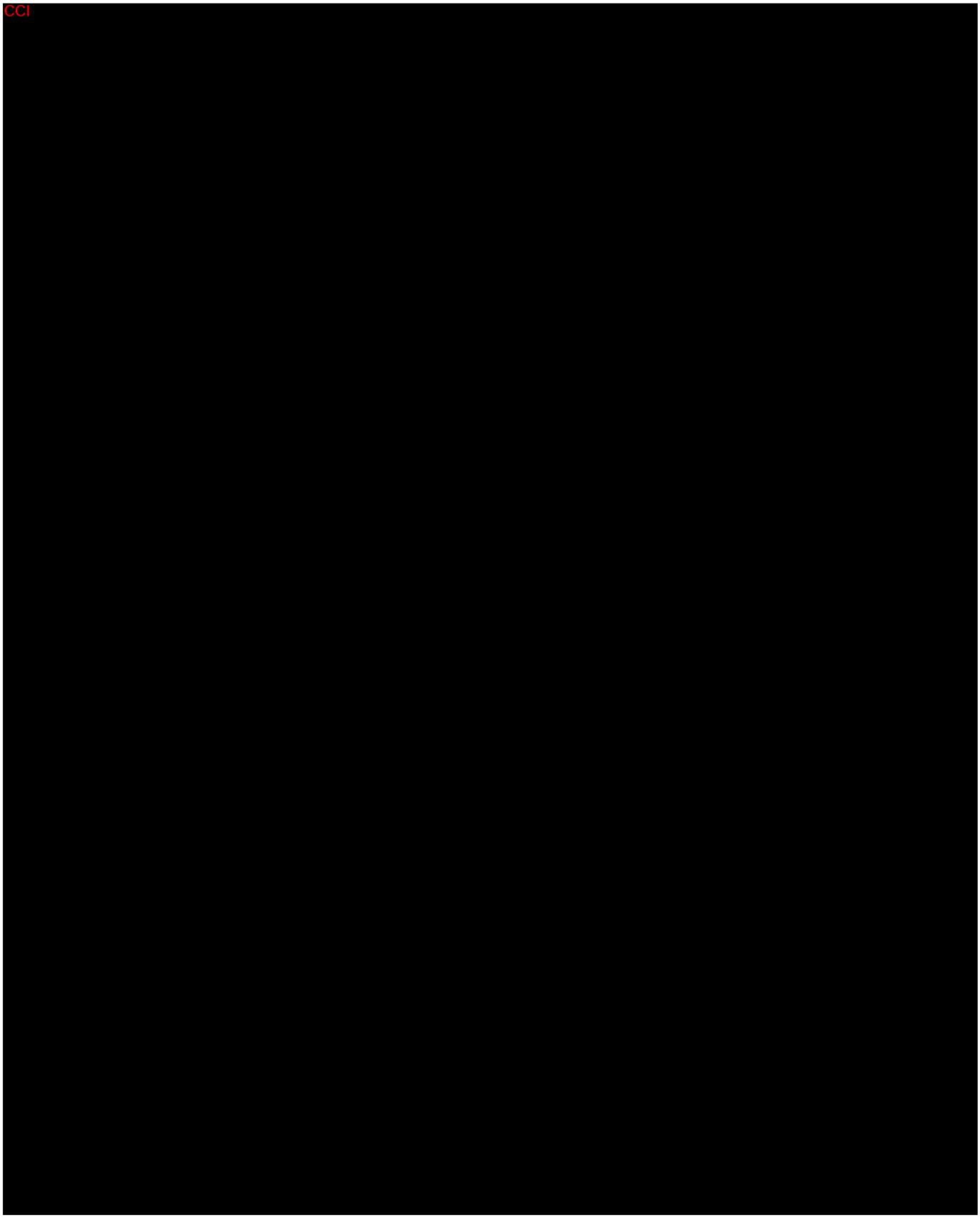



v 29Nov2020 Page 3 of 3


CCI

CCI

[redacted]


CCI

CCI

[redacted]

CCI

[redacted]

CCI

***Thank you for completing these questions!***

CCI

## 19.3 Appendix 3: Baseline Diet Assessment

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

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

   If Yes, what is the diet?

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

   ☐ 6-food or 3 Food Elimination Diet

   ☐ Supplemental Protein Shake/drink specify: _____

   ☐ Other; describe: _____

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

   If Yes, what are they? _____

   _____

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

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

| Food or Type of Food | Effect |
|---|---|
| | |
| | |
| | |

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

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

   _____

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

   ☐ Milk ☐ Egg ☐ Wheat ☐ Soy

   **What are the main foods that YOU DO eat?**

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

   _____

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

   If Yes, please describe: _____

   _____

## 19.4 Appendix 4: Common Terminology Criteria for Adverse Events v. 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. | | | | | |

## 19.5 Appendix 5: EGD Histology

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

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

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

**Biopsies will be obtained from the following:**

- **Esophagus** (***only*** if the subject has a history of concomitant EoE, if esophagus looks suspicious for EoE or if patient is symptomatic on screening dysphagia question)
  - A set of 2 fragments from the distal esophagus
  - A set of 2 fragments from the mid-proximal esophagus.
  - Up to 2 extra specimens may be collected if there are any additional areas of interest

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

- **Stomach**
  - A set of 4 specimens from separate areas of the gastric antrum (2–5 cm proximal to the pylorus)
  - A set of 4 specimens from separate areas of the gastric corpus (2 from the proximal lesser curvature and 2 from the greater curvature)
  - Up to 2 extra specimens may be collected if there are any additional areas of interest

  A count of ≥30 eosinophils/hpf in at least 5 hpf will be considered diagnostic of eosinophilic gastritis (EG) for the purposes of the study.

- **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.

## 19.5 Appendix 5: EGD Histology cont.

A count of ≥30 eosinophils/hpf in at least 3 hpf will be considered diagnostic of eosinophilic duodenitis (EoD) for the purposes of the study.

A count of ≥30 eosinophils/hpf in at least 5 hpf in the stomach ***and*** ≥30 eosinophils/hpf in at least 3 hpf in the duodenum will be considered diagnostic of eosinophilic gastritis/ duodenitis (EG/EoD) for the purposes of the study.

**The following will be reported for esophageal biopsies:**

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

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

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

**The following will be reported for gastric biopsies:**

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

## 19.5 Appendix 5: EGD Histology cont.

**The following will be reported for duodenal biopsies:**

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

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

## 19.6 Appendix 6: Sampson's Criteria of Anaphylaxis

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

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

**OR**

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

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

## 19.7 Appendix 7: ePRO Teaching Tool

**PROTOCOL AK002-016**
**PROTOCOL AK002-016X**

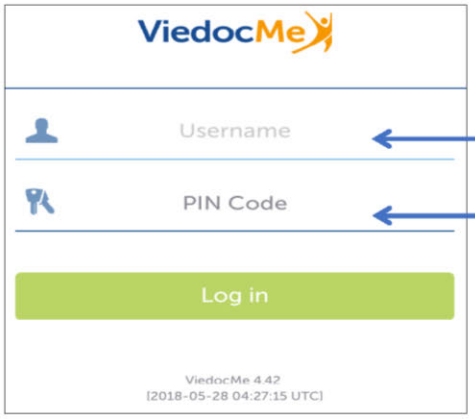
Allakos

**INSTRUCTIONS FOR COMPLETION OF ELECTRONIC QUESTIONNAIRES**

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

**TO ACCESS THE ELECTRONIC QUESTIONNAIRES**

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




**LOGGING IN TO ViedocME**

Enter 6-digit Username provided by Study Coordinator

Enter 4-digit PIN provided by Study Coordinator

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

**REMINDERS FROM ViedocME FOR COMPLETION OF DAILY QUESTIONNAIRES**

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

Version 11Apr2021 Page **1** of **4**

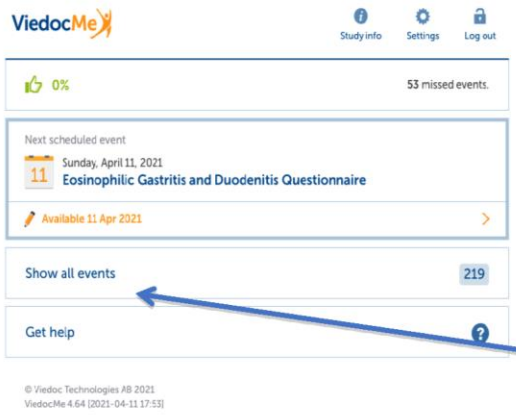
## 19.7 Appendix 7: ePRO Teaching Tool cont.

**PROTOCOL AK002-016**
**PROTOCOL AK002-016X**

Allakos

**THINGS TO REMEMBER WHEN COMPLETING THE QUESTIONNAIRES**

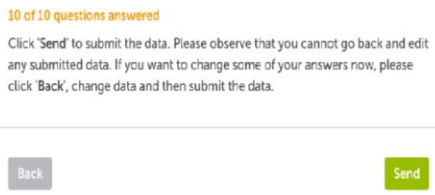
- When you first log on to ViedocME the HOME screen will display the 1st questionnaire that is due for the day, which is usually the 10-question EG/EoD Questionnaire as shown below:




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

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

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




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

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

**COMPLETING THE DAILY QUESTIONNAIRES DURING THE STUDY**

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

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

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

Version 11Apr2021 Page **2** of **4**

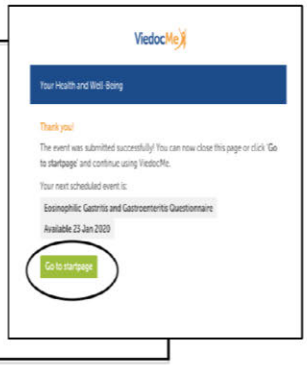
## 19.7 Appendix 7: ePRO Teaching Tool cont.

**PROTOCOL AK002-016**
**PROTOCOL AK002-016X**

Allakos

**IT IS IMPORTANT:**

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




**STUDY COORDINATORS- COMPLETE THIS UPON ViedocME ACTIVATION:**

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

**Username:** _____

**PIN (don't share with others):** _____

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

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

*For each medical history condition of AD or asthma that you have, you will receive 1 "Additional Question" daily. During the screening period you will receive the Dysphagia question and this will continue during the study if you have symptoms of dysphagia (trouble swallowing).
As noted above, the "Additional Question(s)" will only populate AFTER you have completed the daily EG/EoD PRO Questionnaire. You must hit SEND & GO TO STARTPAGE to see all questionnaires.

**START DIARY TODAY!**

**Additional Information regarding diary completion on Page 4!**

Version 11Apr2021 Page **3** of **4**

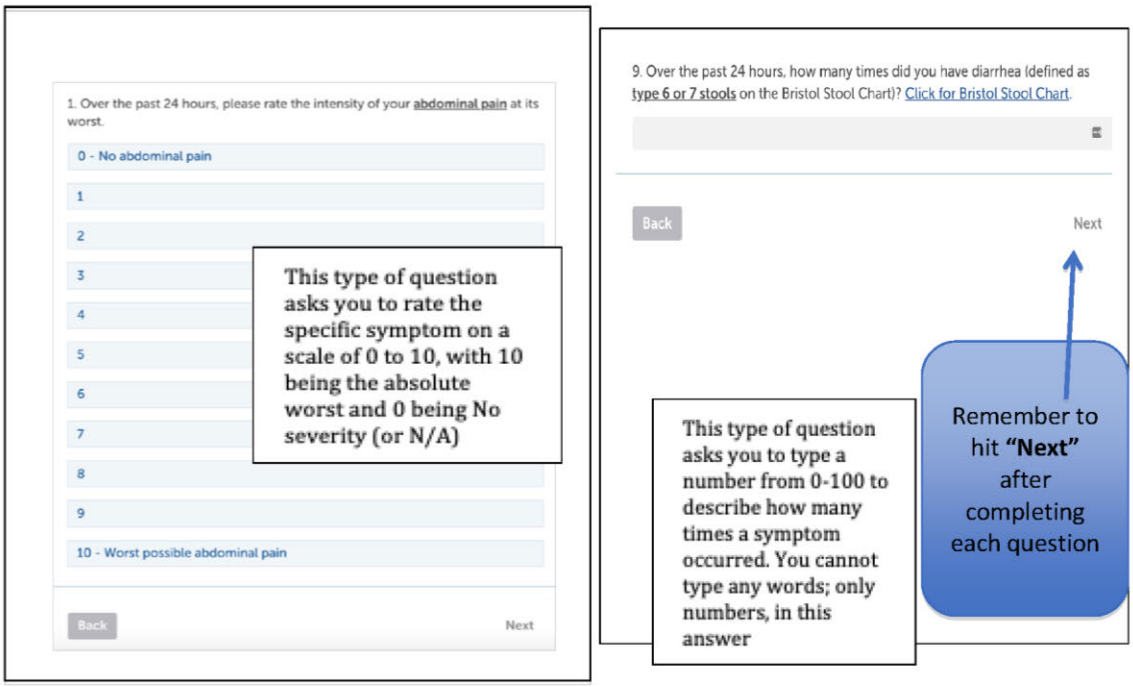
## 19.7 Appendix 7: ePRO Teaching Tool cont.

**PROTOCOL AK002-016**
**PROTOCOL AK002-016X**

Allakos

**TYPES OF QUESTIONS ON EG/EoD QUESTIONNAIRE**

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




**HOW TO ANSWER THE ViedocME QUESTIONS**

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

EXAMPLE:

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

**WHAT TO DO IF YOU WILL BE WITHOUT INTERNET ACCESS**

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

Version 11Apr2021 Page **4** of **4**

CCI

[redacted]

CCI

[redacted]

## 19.10 Appendix 10: Additional Questions for Atopic Conditions

PID: _____

Date: _____

ADDITIONAL QUESTION(S)

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

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

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

v. 17Mar2020 Page 1 of 1

## 19.11 Appendix 11: Previous Treatments Review

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

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

2. Have you previously taken prescription medications specifically for the diagnosis of EG/EoD? Yes* ☐ No ☐ N/A, not previously diagnosed with EG/EoD ☐

   If yes*please list:_____

   *All medications taken for EG/EoD or EG/EoD symptoms at any time should be listed on the Con-Med Log.*

3. Have you previously taken over-the-counter (OTC) medications for symptoms of EG/EoD (i.e., Zantac®, Tylenol®, Tums®)? Yes* ☐ No ☐

   If yes*please list:_____

   *All medications taken for EG/EoD symptoms at any time should be listed on the Con-Med Log.*

4. Have you previously tried changing your diet to help improve the symptoms of EG/EoD? Yes* ☐ No ☐

   If yes*please describe:_____

5. Have you previously tried changing your eating habits to help improve the symptoms of EG/EoD? Yes* ☐ No ☐

   If yes*please describe:_____

6. Have you previously tried other methods to help improve the symptoms of EG/EoD (i.e., acupuncture, pressure point therapy)? Yes* ☐ No ☐

   If yes*please describe:_____

**Additional Comments**

_____

_____

_____

Name of Person completing the **Previous Treatments Review**

## 19.12 Appendix 12: Hepatitis B and Hepatitis C Serological Testing Details

### 19.12.1 Hepatitis B Testing

HBsAg positive patients are excluded. However, in case of past infections/vaccination in order to qualify, the patient's testing status needs to align with the information in Table 5.

**Table 5 Hepatitis B Reflex Testing**

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

### 19.12.2 Hepatitis C Testing

Anti-HCV positive and HCV-RNA positive patients are excluded. In order to qualify, the patient's testing status needs to align with the information in Table 6.

**Table 6 Hepatitis C Reflex Testing**

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