A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacodynamic Effect of AK002 in Patients with Eosinophilic Gastritis and/or Eosinophilic Gastroenteritis

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

# Clinical Research Protocol AK002-003

## A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacodynamic Effect of AK002 in Patients with Eosinophilic Gastritis and/or Eosinophilic Gastroenteritis

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| Investigational Product | AK002 | |
| Study Phase | 2 | |
| Sponsor | Allakos, Inc.<br>975 Island Drive, Suite 201, Redwood City, CA 94065 USA | |
| Medical Monitor | Name: [redacted], MD, PhD<br>Telephone: [redacted]<br>E-mail: [redacted] | |

**Approval:**

[redacted]

[redacted], MD, PhD, [redacted] — 7 FEB 2019 (Date)

# 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:** AK002-003

**IND:** 135158

**Protocol Title:** A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacodynamic Effect of AK002 in Patients with Eosinophilic Gastritis and/or Eosinophilic Gastroenteritis

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**Amendment 6:** **07 February 2019**

**Investigator:** _____

**Printed Name:** _____

**Signature:** _____

**Date:** _____

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## List of Abbreviations

| | |
|---|---|
| ACE | Angiotensin-converting enzyme |
| ADCC | Antibody-dependent cellular cytotoxicity |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| Anti-IL-5 | Anti-interleukin-5 |
| AST | Aspartate aminotransferase |
| ATC | World Health Organization Anatomical Therapeutic Chemical Classification System |
| BMI | Body mass index |
| C | Centigrade |
| CBC | Complete blood count |
| CFR | Code of Federal Regulation |
| cm | Centimeter |
| CMH | Cochran-Mantel-Haenszel |
| CSI | Composite score of interest |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CU | Chronic Urticaria |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture (system) |
| EG | Eosinophilic gastritis |
| EGD | Esophago-gastro-duodenoscopy |
| EGE | Eosinophilic gastroenteritis |
| EGID | Eosinophilic gastrointestinal disorders |
| [redacted] | [redacted] |
| EMT | Epithelial mesenchymal transition |
| EoE | Eosinophilic esophagitis |
| ET | Early Termination |
| FDA | Food and Drug Administration |
| FSH | Follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| HEENT | Head, eyes, ears, nose, and throat |
| HES | Hypereosinophilic Syndrome |
| HIPAA | Health Insurance Portability and Accountability Act |
| HPF | High power field |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation |
| iDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IgE | Immunoglobulin E |

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|---|---|
| IgG1 | Immunoglobulin G1 |
| IgG4 | Immunoglobulin G4 |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| IRR | Infusion-Related Reaction |
| ISM | Indolent systemic mastocytosis |
| IRT | Interactive Response Technology |
| ITIM | Immunoreceptor Tyrosine-based inhibitory motif |
| IUD | Intrauterine device |
| IV | Intravenous |
| kg | Kilogram |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |
| MITT | Modified Intention-to-Treat (population) |
| mM | Millimolar |
| mL | Milliliter |
| MTD | Maximum tolerated dose |
| NaCl | Sodium chloride |
| NK | Natural killer |
| PCP | Primary care physician |
| PD | Pharmacodynamics |
| PE | Physical examination |
| PID | Patient identification number |
| PK | Pharmacokinetic(s) |
| PPI | Proton pump inhibitor |
| QOL | Quality of life |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| [redacted] | [redacted] |
| Siglec | Sialic acid-binding, immunoglobulin-like lectin |
| SOC | System organ class |
| TEAE | Treatment-emergent adverse event |
| TEAESI | Treatment-emergent adverse event of significant interest |
| TNF | Tumor necrosis factor |
| TSS | Total symptom score |
| ULN | Upper limit of normal |
| VAS | Visual analog scale |
| WBC | White blood cell |
| WHODD | World Health Organization Drug Dictionary |
| w/v | Weight/volume |

## 1. Protocol Synopsis

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| **Study Title** | A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacodynamic Effect of AK002 in Patients with Eosinophilic Gastritis and/or Eosinophilic Gastroenteritis |
| **Sponsor** | Allakos, Inc., 975 Island Drive, Suite 201, Redwood City, CA 94065 USA |
| **Number of Sites** | Approximately up to 25 clinical centers in the US |
| **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 eosinophils, mast cells and, at lower levels, on basophils. Binding of AK002 to Siglec-8 induces a signal that inhibits mast cell activation and can lead to apoptosis in eosinophils. In the presence of effector cells (such as natural killer cells), AK002 binding to Siglec-8 depletes circulating eosinophils by antibody-dependent cell-mediated cytotoxicity (ADCC). This profile of activity may provide clinical benefit in diseases in which these cell types play a role, such as Eosinophilic Gastritis (EG) and/or Eosinophilic Gastroenteritis (EGE). |
| **Clinical Background** | Single doses of 0.0003–1 mg/kg AK002 were previously tested in healthy volunteers and single doses of 0.001–1 mg/kg were previously tested in patients with indolent systemic mastocytosis (ISM). Multiple doses of 0.3 mg/kg have been given to healthy volunteers, and multiple doses of 1, 3, 6, and 10 mg/kg have been given to ISM patients. In addition, multiple doses of 1 mg/kg and 3 mg/kg have been given to patients with chronic urticaria (CU) and severe allergic eye disease. In these studies, AK002 pharmacodynamic (PD) activity was observed for prolonged periods of time and the AK002 pharmacokinetic (PK) parameters demonstrated a half-life amenable to administration every 4 weeks. In ISM patients, monthly infusions of 1 mg/kg and 3 mg/kg have been administered for up to 6 months. Single doses of 1 mg/kg of AK002 suppressed blood eosinophils for up to 84 days in healthy volunteers and in patients with ISM, CU, and severe allergic eye disease. To date, 51 healthy volunteers (36 AK002, 15 placebo), 25 ISM patients, 48 CU patients, and 30 allergic eye disease patients have been enrolled into these clinical studies.<br><br>In general, AK002 was well tolerated. Infusion-related reactions were observed in healthy volunteers, ISM patients receiving a first dose of ≥0.1 mg/kg, and CU and allergic eye disease patients receiving a first dose of either 0.3 mg/kg or 1 mg/kg. Common symptoms of infusion-related reactions were headache, nausea, sweating, flushing and redness. Infusion-related reactions (IRRs) occurring during the infusion could be managed by slowing or temporary interruption of the infusion, with minimal intervention in almost all cases. |

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| **Clinical Background cont.** | The most common treatment-emergent adverse events (TEAEs) observed were headache, respiratory infection, nausea, somnolence, lower back pain, sore throat, throat tightness, nasal congestion, and light tachycardia. 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 adverse event, and a sustained suppression in eosinophils that was consistent with the mechanism of action of AK002. No clinically significant changes in vital signs, electrocardiograms (ECGs), clinical laboratory parameters and physical examination were observed. |
| **Target Disease Background and Rationale** | EG and EGE represent rare types of eosinophilic gastrointestinal disorders (EGIDs) and are characterized by chronic inflammation due to patchy or diffuse infiltration of eosinophils into layers of the stomach (EG) and/or small intestine (EGE) (Prussin, 2014; Reed, 2015; Zhang, 2017). Diagnosis is made based on clinical presentation (gastrointestinal symptoms) combined with increased tissue eosinophils in biopsy specimens from the stomach and duodenum, without any other cause for the eosinophilia. The gastrointestinal symptoms are believed to be due to the release of inflammatory mediators from activated eosinophils, and possibly mast cells, and may vary depending on the layer and/or location of the eosinophilic infiltrate. Symptoms commonly include nausea, vomiting, abdominal pain, diarrhea, bloating, early satiety, and weight loss (Alhmoud, 2016; Lopez-Medina, 2015; Mansoor, 2017; Reed, 2015). Jensen et al. (2016) estimated the prevalence of EG and EGE to be 6.3/100,000 and 8.4/100,000 respectively (for patients ages 1–64 years old). Mansoor et al. (2017) estimate the overall prevalence of EG to be 5.1/100,000 persons.<br><br>There are no FDA-approved treatments for EG and/or EGE. Current therapies and disease management includes proton pump inhibitors, restricted/elemental diets, systemic or oral 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 EGE, although partial benefit can be observed in patients with eosinophilic esophagitis (EoE) (Katz, 2013). Restricted/elemental diets are not considered sustainable for long-term treatment and are used more so to provide nutrition, despite continuing symptoms. Corticosteroids, systemic or oral, can provide symptom relief, but are not a solution for long-term treatment due to their numerous side effects.<br><br>By reducing the number of blood and tissue eosinophils and reducing the number and/or activation of tissue mast cells, AK002 may be useful in the treatment of patients with EG and/or EGE.<br><br>The proposed AK002 doses of 0.3 mg/kg administered for the first infusion, 1 mg/kg administered for the second infusion, followed by a dose of either |

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| **Rationale for Dose Selection** | 1 mg/kg or 3 mg/kg administered every 4 weeks for 2 subsequent infusions is based on prior experience with AK002 in healthy volunteers and in patients with ISM, CU, and allergic eye disease. [redacted]. A starting dose of 0.3 mg/kg with a second dose of 1 mg/kg, followed by a dose of either 1 mg/kg or 3 mg/kg for subsequent infusions, therefore, has been chosen for this Phase 2 study with AK002 in patients with EG and/or EGE. |
| **Rationale for Number of Subjects** | Approximately 60 patients will be randomized 1:1:1 to receive 1 of 3 dose regimens in a double-blind fashion: placebo; an initial 0.3 mg/kg AK002 dose, followed by 3 doses of 1 mg/kg AK002 given every 4 weeks; or an initial 0.3 mg/kg AK002 dose, a second dose of 1 mg/kg, followed by 2 doses of 3 mg/kg AK002 given every 4 weeks. |
| **Study Design** | This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability, and pharmacodynamic effect of AK002 in patients with EG and/or EGE.<br><br>Screening data will be reviewed to determine patient eligibility. Patients with EG and/or EGE who meet all inclusion criteria and none of the exclusion criteria are eligible to be enrolled into the study. Subjects who do not meet all eligibility criteria at screening, or who qualify at screening but are not enrolled, may be assigned a new Patient ID number and re-screened once. Subjects re-screened within 30 days of signing the initial consent will not need to sign a new ICF provided there have been no changes to the ICF.<br><br>The study is designed as follows:<br>• A 14 to 35-day screening period with baseline evaluations for study eligibility, including baseline active symptoms of disease (gathered by PRO completed during screening) and Esophago-Gastro-Duodenoscopy (EGD) with biopsy. |

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| **Study Design cont.** | • If subjects meet histology and symptom eligibility criteria, they will receive 4 doses of AK002 or placebo by IV infusion on Days 1, 29 (±3), 57 (±3), and 85 (±3).<br>• A repeat EGD with biopsy will be performed on Day 99 (±3) or approximately 2 weeks after last dose of study drug if subject is terminated early.<br>• Subjects will be followed for 56 (±3) days after the last dose. Follow-up visits will occur on Days 113 (±3) and 141 (±3).<br>• If the absolute lymphocyte and/or eosinophil counts have not recovered at Day 141, the follow-up period will be extended, and subjects will be followed until the counts have recovered. During the extended follow-up period, subjects will return to the site every 28 days (±3) for a follow-up safety visit.<br>• Total study duration is up to approximately 23–25 weeks (study duration could be extended, as described above, if the absolute lymphocyte and/or eosinophil counts have not recovered).<br>Pre-study medications and pre-existing dietary restrictions should remain unchanged throughout the study. Subjects will undergo a standardized baseline evaluation of eating habits, food habits/restrictions, and food avoidance behaviors and will be asked to maintain similar habits and restrictions throughout the study.<br>Subjects who complete through Day 113 may have the option to receive AK002 in a separate open-label extension study, if all eligibility criteria for the extension study are satisfied. Subjects who enroll in the AK002-003X extension study will begin extension study dosing immediately after completing the Day 113 visit of this protocol. Subjects will not complete the Day 141 procedures or extended follow-up under the AK002-003 protocol. Open-label dosing and follow-up including any extended follow-up required to monitor the recovery of lymphocytes and eosinophils will occur under the AK002-003X extension study. |
| **Primary Objectives** | The primary objectives of the study are to evaluate:<br>1) The efficacy of AK002 in patients with EG and/or EGE as estimated by the number of eosinophils per high power field (HPF) in gastric and/or duodenal biopsies before and after receiving AK002 or placebo.<br>2) The safety and tolerability of AK002 in patients with EG and/or EGE. |
| **Secondary Objectives** | The secondary objectives are to evaluate the effects of AK002 in patients with EG and/or EGE by comparing AK002 to placebo treatment for the following parameters: |

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| **Secondary Objectives cont.** | 1) Changes in symptoms of EG and EGE in a patient reported outcome (PRO) questionnaire.<br>2) Change in [redacted].<br>3) Compare responders between AK002 and placebo; a responder is a patient who exhibits a >30% reduction in CSI (abdominal pain, nausea, and diarrhea) and a >75% reduction in mucosal eosinophils. |
| **Exploratory Objectives** | The exploratory objectives are to evaluate the effect of AK002 in patients with EG and/or EGE by comparing AK002 to placebo treatment for the following parameters: |
| **Exploratory Objectives cont.** | 1) Number of [redacted] in patients with [redacted].<br>2) [redacted] before and after treatment.<br>3) Change in [redacted], respectively.<br>4) Change in [redacted].<br>5) Change in [redacted] and [redacted].<br>6) Scoring of [redacted] using the [redacted]. |
| **Safety Objectives** | To evaluate the safety and tolerability of AK002 in patients with EG and/or EGE by determining AE incidence and severity, study withdrawals due to AEs, changes in vital signs and laboratory tests, changes in concomitant medication use due to AEs, and other safety parameters. |
| **Safety Endpoints** | The safety and tolerability of AK002 will be assessed by determining the incidence, relationship to study drug, and severity of TEAEs, withdrawals due to AEs, and changes in vital signs, laboratory tests, changes in concomitant medication use due to AEs, immunogenicity and other safety parameters. |
| **Efficacy Endpoints** | • Percent change from baseline in the number of eosinophils in gastric mucosa or duodenal mucosa.<br>• Gastrointestinal symptomatology (PRO questionnaire)<br>– Abdominal pain<br>– Nausea<br>– Vomiting<br>– Diarrhea<br>– Abdominal cramping<br>– Bloating<br>– Early satiety<br>– Loss of appetite |

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| **Efficacy Endpoints cont.** | • Change from baseline in number of eosinophils in gastric mucosa in patients with EG.<br>• Change from baseline in number of eosinophils in duodenal mucosa in patients with EGE.<br>• Compare responders between AK002 and placebo; a responder is a patient who exhibits a >30% reduction in CSI (abdominal pain, nausea and diarrhea) and a >75% reduction in mucosal eosinophils.<br>• Change from baseline in [redacted] absolute counts.<br>• [redacted] |
| **Study Population** | Adult male and female patients with EG and/or EGE |
| **Patient Selection Criteria** | **Inclusion Criteria**<br>Patients with EG and/or EGE are eligible to enroll in the study if all of the following criteria are met:<br>1) Male or female aged ≥18 and ≤80 years at the time of signing ICF.<br>2) Average weekly score of ≥3 (on a scale from 0–10) recorded for either abdominal pain, diarrhea, and/or nausea on the PRO questionnaire during at least 2 weeks or 2 of the last 3 weeks of PRO collection. A minimum of 4 questionnaires must be completed each qualifying week.<br>3) Eosinophilia of the gastric mucosa ≥30 eosinophils/HPF in 5 HPFs and/or eosinophilia of the duodenal mucosa ≥30 eosinophils/HPF in 3 HPFs from the EGD performed during the screening period, without any other cause for the gastric eosinophilia (e.g., parasitic or other infection or malignancy).<br>4) Subjects must have failed or not be adequately controlled on standard of care treatments for EG or EGE symptoms (which could include PPIs, systemic or topical corticosteroids, and/or diet, among others).<br>5) If on other treatments for EG, EGE, or EoE at enrollment, stable dose for at least 5 half-lives prior to screening and willingness to continue on that dose for the duration of the study.<br>6) If patient is on pre-existing dietary restrictions, willingness to maintain dietary restrictions throughout the study, as much as possible.<br>7) Able and willing to comply with all study procedures.<br>8) Female subjects must be either post-menopausal for at least 1 year with FSH level >40 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. |

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| **Patient Selection Criteria cont.** | **Inclusion Criteria cont.**<br>Male subjects 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 at any time during study participation.<br>**Exclusion Criteria**<br>Subjects will be excluded from the study if they meet any of the following criteria:<br>1) Known hypersensitivity to any constituent of the study drug.<br>2) Diagnosis of celiac disease or active *H. pylori* infection as determined by screening EGD or a history of celiac disease diagnosed by prior EGD.<br>3) Presence of abnormal laboratory values considered by the Investigator to be clinically significant.<br>4) Grade 2 or higher lymphopenia ($<0.8 \times 10^9$/L lymphocytes).<br>5) Any disease, condition (medical or surgical), or cardiac abnormality, which, in the opinion of the Investigator, would place the subject at increased risk.<br>6) History of malignancy; except carcinoma in situ, early stage prostate cancer, or non-melanoma skin cancers. However, cancers that have been in remission for more than 5 years and are considered cured, can be enrolled (with the exception of breast cancer). All history of malignancy (including diagnosis, dates, and compliance with cancer screening recommendations) must be documented and certified by the Investigator, along with the statement that in their clinical judgment the tissue eosinophilia is attributable to EGID, rather than recurrence of malignancy.<br>7) Treatment with chemotherapy or radiotherapy in the preceding 6 months.<br>8) Treatment for a clinically significant helminthic parasitic infection within 6 months of screening and/or a positive helminthic test at screening.<br>9) Use of any medications that may interfere with the study such as immunosuppressive or immuno-modulatory drugs (including azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, tacrolimus, anti-TNF, anti-IL-5, anti-IL-5 receptor, dupilumab, anti-IgE antibodies, omalizumab) or systemic corticosteroids with a daily dose >10 mg of prednisone or equivalent, during 5 half-lives prior to screening or during the screening period, except for omalizumab taken for asthma and/or urticaria when their asthma and/or urticaria cannot be controlled on other medications, If on omalizumab, the dose must have been stable for at least 4 weeks prior to screening. |

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| **Patient Selection Criteria cont.** | **Exclusion Criteria cont.**<br>10) 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 of the study drug administration.<br>11) Known history of alcohol, drug, or other substance abuse or dependence.<br>12) Participation in a concurrent interventional study with the last intervention occurring within 30 days prior to administration of study drug (or 90 days or 5 half-lives, whichever is longer, for biologic products).<br>13) Women who are pregnant, breastfeeding, or planning to become pregnant while participating in the study.<br>14) Any other reason that, in the opinion of the Investigator or Medical Monitor makes the patient unsuitable for enrollment.<br>15) Diagnosis of Hypereosinophilic Syndrome (HES), based on standard criteria (blood eosinophils >1500/µL with involvement of either the heart, nervous system, and/or bone marrow). |
| **Test Product, Dose, and Administration** | AK002 [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 through an infusion pump, as specified in the Pharmacy Manual.<br>AK002 and placebo are formulated in [redacted] pH 6.0, in water for injection.<br>AK002 at a dose of 0.3 mg/kg or placebo will be prepared according to subject's body weight and administered on Day 1. Subsequent infusions of AK002 at a dose of 1 mg/kg or 3 mg/kg or placebo will be prepared on Day 29 (±3), Day 57 (±3), and Day 85 (±3). The initial infusion should be given over at least a 5-hour period, and the second and third infusions should be given over at least a 4-hour period. The last infusion can be given over approximately 3–5 hours, depending on the subject's tolerance of the previous infusions and at the Investigator's discretion. |
| **Duration of Subject Participation** | The total study duration for each subject will be approximately 23–25 weeks. (Study duration could be extended, as described above, if the absolute lymphocyte and/or eosinophil counts have not recovered.) This includes:<br>• A screening period of 14–35 days prior to study drug administration.<br>• A treatment period of 85 days (±3 days).<br>• A follow-up period of 56 days (±3 days) following last dose of AK002 (or until lymphocyte and eosinophil counts have recovered, if not recovered during the 56-day follow-up period).<br>• After the follow-up period ends on Day 141 or at Early Termination, if the lymphocyte and/or eosinophil counts have not recovered, the subject will enter the Extended Follow-Up period. |

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| **Duration of Subject Participation cont.** | • Subjects who enroll in the AK002-003X extension study will participate in the AK002-003 study for 19-21 weeks and will complete the study through the Day 113 Visit. Subjects will not complete the Day 141 procedures or extended follow-up under the AK002-003 protocol. |
| **Safety Evaluations** | Safety and tolerability will be assessed throughout the study by monitoring and evaluating adverse events (AEs), including any complications resulting from the IV infusion. All TEAEs will be collected from the start of study drug administration through Day 113 if enrolling in the AK002-003X extension study, Day 141 (±3 days) or Early Termination (ET).<br><br>Severity of Adverse Events will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (or most current version). All AEs will be assigned a severity grade and will be assessed to determine whether they are clinically significant and related to study drug.<br><br>Additional safety evaluations include clinical laboratory tests, including anti-drug antibody (ADA) to AK002, complete blood counts, chemistries, and urinalyses as well as physical exams (PEs) and vital signs findings.<br><br>The Medical Monitor will review blinded safety data as it accumulates. The unblinded safety monitor will review unblinded safety data as it accumulates and escalate to the Medical Monitor as appropriate.<br><br>An independent Data Monitoring Committee (iDMC) has been convened and will meet at regularly scheduled intervals in accordance with the iDMC charter.<br><br>During the period of Extended Follow-Up, data collection will be limited to hematology, SAEs, and Adverse Events of Special Interest. |
| **Efficacy and Pharmacodynamic Evaluations** | Number of eosinophils in gastric and duodenal mucosa will be evaluated. In addition, the number of [redacted] will be evaluated in patients with [redacted]<br><br>The [redacted] will be collected.<br><br>Daily self-administration of a disease-specific patient questionnaire [PRO Questionnaire] will be used to evaluate signs and symptoms associated with EG and/or EGE.<br><br>For subjects 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 subjects with [redacted], evaluation will include a question about the [redacted] over the past 24 hours.<br><br>Subjects will rate their quality of life using the non-disease-specific [redacted] at various study visits. |

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| **Pharmacokinetic Evaluations** | Blood (serum) will be collected for assessment of AK002 concentrations using a validated enzyme-linked immunosorbent assay (ELISA) method. Pharmacokinetic (PK) blood samples will be obtained during the screening period and pre-dose on Days 29, 57, and 85, and additionally on Days 15, 113, and 141 (or E/T). Blood (serum) will be collected for assessment of AK002 anti-drug-antibodies (ADA) using a validated assay method. ADA blood samples will be obtained during the screening period, on Days 15, 29, 57, and 85, and Day 141 (or E/T), as well as any time an immunogenicity-related AE occurs. |
| **Statistical Analysis** | All subjects who received study medication will be included in the Safety population for safety analysis. Subjects who are randomized and have received at least one dose of study medication and have a post-baseline PD or efficacy assessment will be included in the Modified Intent-to-Treat (MITT) population for efficacy analysis.<br><br>The study statistician along with the study team will review protocol deviations to identify subjects to be excluded from the efficacy analysis. All subject data will be listed.<br><br>When appropriate, summary statistics will be provided (number of non-missing values, mean, median, standard deviation, minimum, and maximum for continuous variables and number and percentage of subjects for categorical variables) by treatment group for all measures, including demographic and baseline assessments, safety, PD evaluations, and efficacy endpoints. Baseline for all safety and efficacy endpoints is defined as the last observations before administration of the first IV infusion of study drug, unless otherwise specified. No imputation will be used for missing data.<br><br>Subjects will be stratified at randomization based on the highest weekly average of the qualifying symptom of disease recorded on the PRO questionnaire during the screening period, to 1 of 2 groups, namely PRO score 3.0–4.9 or 5.0–10.0.<br><br>**Efficacy Analysis:** The primary endpoint is the percent change from baseline in the number of eosinophils per HPF in gastric or duodenal mucosa. For subjects 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 99. For subjects who provide both gastric and duodenal biopsies, the calculation will be based on the average count of the highest readings from the combined pool of gastric and duodenal mucosa. This endpoint will be summarized by treatment group. Between dose and placebo group comparisons in the percent change will be carried out by analysis of covariance (ANCOVA) with baseline value and randomization stratum as covariates. Sensitivity analyses will be carried out to demonstrate the robustness of the treatment effect. |

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| **Statistical Analysis cont.** | Gatekeeping procedure is added for multiplicity adjustment due to the comparisons of 2 dose groups to the placebo group.<br><br>Method of multiple imputations for missing data is added to the primary endpoint and the first secondary endpoint analyses.<br><br>The total symptom score (TSS), the composite score of interest (CSI), and domain scores of the PRO symptom intensities will be summarized weekly for each patient. The weekly change scores will be analyzed using the MMRM model with treatment, visit, and treatment-by-visit interaction as fixed factors, baseline as covariates, and subject as repeated measure unit. The comparison between the active dose and placebo groups will be based on the averages of the last 6 weeks (Weeks 9 through 14), and the last 2 weeks (Weeks 13 and 14) prior to biopsy, for weekly TSS, CSI, and symptom scores using simple contrasts. Details of the analytical methods will be included in the Statistical Analysis Plan (SAP).<br><br>A responder analysis comparing AK002 and placebo will be performed. A responder is a patient who exhibit a >30% reduction in CSI (abdominal pain, nausea, and diarrhea) and a >75% reduction in mucosal eosinophils.<br><br>Baseline for PRO will be calculated using all PRO assessments collected prior to randomization.<br><br>Change in the number of [redacted] from baseline will be analyzed using the same MMRM method.<br><br>**Safety Analysis:** Safety measures including AEs, infusion-related reactions, clinical laboratory tests (including anti-AK002 antibodies), vital signs, physical exams, and concomitant medication usage will be summarized descriptively by treatment group and study visit, as appropriate. Shift tables will be created as applicable.<br><br>**Sample Size:** Assuming a reduction of 30% in the number of eosinophils per HPF (primary endpoint) from baseline in the AK002 treated group versus a 10% reduction per HPF in the placebo group, assuming a standard deviation of 20%, 20 subjects per group would provide 87% power for a two-sided test with a significance level of 0.05. Hence, 20 subjects per group would be more than adequate from the efficacy perspective. |
| **Rationale for Protocol Amendment 6** | The following modifications have been incorporated into Amendment 6:<br><br>• Updated the corporate address for Allakos.<br><br>• Clarified that Exclusion Criteria #2 applies to active *H. pylori* infection, so that infection can be treated prior to enrollment.<br><br>• Added Exclusion Criteria #15 of Hypereosinophilic Syndrome (HES).<br><br>• Updated Exclusion Criteria #6 to reflect that carcinoma in situ is not exclusionary, as it is not considered to be cancer. |

| | |
|---|---|
| **Rationale for Protocol Amendment 6 cont.** | • Updated Inclusion Criteria #2 so that if a subject has 2 qualifying weeks of PROs, they may enter the study without a third week of PROs.<br>• Added a new Study Withdrawal criterion: Subjects, who entered the study with eosinophil levels >1500/μL at baseline, had an IRR during the first or second infusions, and whose eosinophil count was initially suppressed after study drug but then rebounded to >1500 /μL will be withdrawn from the study at the instruction of the unblinded safety monitor.<br>• Removed the requirement that vital signs need to be completed after the subject has been in the supine position for >5 minutes. The requirement that the subject be supine has been removed since some infusion chairs do not fully recline to a supine position. The subject should be at rest for >5 minutes.<br>• An alternative premedication regimen may be used with the approval of the Allakos Medical Monitor if it is felt that the patient may be at increased risk to experience an infusion-related reaction.<br>• Clarified that the rounding of the total infusion volume by some programmable infusion pumps, an infusion of 99 to 101 mL will be considered a complete infusion and will not be recorded as a deviation from the study.<br>• Removed restriction on coffee consumption on infusion days to be consistent with other protocols and since no safety issues have been observed.<br>• Removed restrictions on strenuous exercise and alcohol consumption prior to blood draws to be consistent with other protocols.<br>• Removed optional Exit Interview on Day 99 as this is being captured in the Extension Study instead.<br>• Added Day 99 blood draw for hematology. |

# 2. Background

## 2.1 Siglec-8 and AK002

Siglec-8, a member of the CD33-related family of sialic acid-binding, immunoglobulin-like lectins (Siglecs), is a transmembrane cell surface protein with restricted tissue distribution, expressed selectively on the surface of eosinophils, mast cells and, at lower levels, on basophils. Siglec-8 contains 3 extracellular immunoglobulin-like domains, a transmembrane region, and a cytoplasmic tail containing 2 tyrosine-based signaling motifs including an immunoreceptor tyrosine-based inhibitory motif (ITIM) with inhibitory function. Engagement of Siglec-8 in mast cells can result in inhibition of mediator release, and in eosinophils can induce apoptosis (Bochner, 2009). AK002 also shows potent antibody-dependent cellular cytotoxicity (ADCC) against Siglec-8-positive target cells in vivo and in vitro.

## 2.2 Overview of Nonclinical Studies

AK002 is a humanized non-fucosylated IgG1 antibody to the inhibitory receptor Siglec-8, present on mast cells, eosinophils and basophils. Binding of AK002 to Siglec-8 induces a signal that inhibits mast cell activation and can lead to apoptosis in eosinophils. In the presence of effector cells (such as natural killer cells), AK002 binding to Siglec-8 depletes circulating eosinophils by ADCC. This profile may provide clinical benefit in diseases in in which these cell types play a role, such as EG and/or EGE.

Siglec-8 is not expressed in species other than humans and therefore two 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 the presence of natural killer cells, AK002 shows potent ADCC activity against mast cells but does not exhibit complement-dependent cytotoxicity in vitro. 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 after 5 weekly doses at these dose levels. There was no evidence of anti-drug antibodies (ADA) in either study. Decreases in eosinophil counts in both sexes were observed, which reflect the expected pharmacology of AK002. The no-observed-adverse-effect-level (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 is being studied in an ongoing first-in-human, open-label Phase 1 study evaluating ascending single doses and multiple doses of AK002 in patients with indolent systemic mastocytosis (AK002-001), and a blinded, placebo-controlled study of ascending single doses of AK002 in healthy volunteers (AK002-002) has also been completed. AK002 is also currently being evaluated in 2 open-label studies, one in chronic urticaria (AK002-006) and one in severe allergic eye disease (AK002-005).

Single doses of 0.0003–1 mg/kg AK002 were previously tested in healthy volunteers and in patients with ISM. Multiple doses of 0.3 mg/kg have been administered to healthy volunteers and multiple doses of 1, 3, 6, and 10 mg/kg AK002 have been administered to ISM patients. In addition, multiple doses of up to 3 mg/kg have been administered to patients with chronic urticaria (CU) and severe allergic eye disease. A number of patients have received up to 6 monthly infusions. In these studies, AK002 pharmacodynamic (PD) activity was observed for prolonged periods of time and the AK002 pharmacokinetic (PK) parameters demonstrated [redacted]. In ISM patients, monthly infusions of 1 mg/kg have been administered for up to 6 months, and monthly infusions of 3 mg/kg have been

administered for up to 4 months. Single doses of 1 mg/kg AK002 [redacted] in healthy volunteers and in patients with ISM, CU, and severe allergic eye disease. To date, 51 healthy volunteers [redacted], 25 ISM patients, 48 urticaria patients, and 30 allergic eye disease patients have been enrolled into these clinical studies.

In general, AK002 was well tolerated. Infusion-related reactions (IRRs) were observed in healthy volunteers, ISM patients receiving a first dose of ≥0.1 mg/kg, and in CU and allergic eye disease patients receiving a first dose of either 0.3 mg/kg or 1 mg/kg. Common symptoms of IRRs were headache, nausea, sweating, flushing, and redness. Infusion-related reactions occurring during the infusion could be managed by slowing or temporary interruption of the infusion, with minimal intervention. In 6 healthy volunteers who received 2 doses of 0.3 mg/kg, 4 weeks apart, the second dose was better tolerated than the first dose. This is also the case so far in the 3 ongoing studies in patients with ISM, CU, and allergic eye disease, with fewer adverse events reported during the second and subsequent infusions, when compared to the first infusion. The most common treatment-emergent adverse events (TEAEs) observed were headache, upper respiratory infection, nausea, somnolence, lower back pain, sore throat, throat tightness, nasal congestion, and light tachycardia. In both healthy volunteers and ISM, CU, and allergic eye disease patients, there was a transient decrease in lymphocyte count after the AK002 infusion (usually resolving within 1 day) that was not associated with any adverse event, and a sustained suppression in eosinophils that was consistent with the mechanism of action of AK002. No clinically significant changes in vital signs, electrocardiograms (ECGs), clinical laboratory parameters, and physical examination were observed.

### 2.4 Eosinophilic Gastrointestinal Disorders

Eosinophilic gastrointestinal disorders (EGIDs) 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 (EG) and eosinophilic gastroenteritis (EGE) represent rare and overlapping type of EGIDs that are distinct from EoE (eosinophilic esophagitis) and EoC (eosinophilic colitis). EG and EGE are characterized by chronic inflammation due to patchy or diffuse infiltration of eosinophils into layers of the stomach (EG) and small intestine (EGE) (Prussin, 2014; Reed, 2015; Zhang, 2017). Eosinophilic infiltration is often found in both the stomach and the small intestine concomitantly (EG and EGE). Diagnosis is made based on clinical presentation (gastrointestinal symptoms) combined with increased tissue eosinophils in biopsy specimens from the stomach and/or duodenum without any other cause for the eosinophilia. The gastrointestinal symptoms are believed to be due to the release of inflammatory mediators from activated eosinophils, and possibly mast cells and may vary depending on the

layer and/or location of the eosinophilic infiltrate in the GI tract. Symptoms commonly include nausea, vomiting, abdominal pain, diarrhea, bloating, early satiety, and weight loss (Alhmoud, 2016; Lopez-Medina, 2015; Mansoor, 2017; Reed, 2015).

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

There are no FDA-approved treatments for EG or EGE. Current therapies and disease management include proton pump inhibitors, antihistamines, restricted/elemental diets, systemic or oral corticosteroids, and occasional off-label use of immunomodulatory biologics (Prussin, 2014; Reed, 2015; Zhang, 2017). Proton pump inhibitors have little to no benefit in patients with EG or EGE, although partial benefit is observed in patients with EoE (Katz, 2013). Restricted/elemental diets are not considered sustainable for long-term treatment and are used more so to provide nutrition, despite continuing symptoms. Corticosteroids, systemic or oral, can provide symptom relief, but are not a solution for long-term treatment due to their numerous side effects.

By reducing the number of blood and tissue eosinophils and reducing the number and/or activation of tissue mast cells, AK002 may be useful in the treatment of patients with EG and/or EGE.

### 3. Rationale for Study and Dose Selection

The proposed AK002 doses of 0.3 mg/kg administered for the first infusion, 1 mg/kg administered for the second infusion, followed by a dose of either 1 mg/kg or 3 mg/kg administered every 4 weeks for 2 subsequent infusions is based on prior experience with AK002 in healthy volunteers and in patients with ISM, urticaria, and/or allergic eye disease.

[redacted] A starting dose of 0.3 mg/kg, with a second dose of 1 mg/kg, followed by a dose of either 1 mg/kg or 3 mg/kg for subsequent infusions, therefore, has been chosen for this Phase 2 study with AK002 in patients with EG and/or EGE.

## 4. Study Objectives

### 4.1 Primary Objective

The primary objectives of the study are to evaluate:

1) The efficacy of AK002 in patients with EG and/or EGE as estimated by the number of eosinophils, per HPF in gastric and/or duodenal biopsies before and after receiving AK002 or placebo.
2) The safety and tolerability of AK002 in patients with EG and/or EGE.

### 4.2 Secondary Objectives

The secondary objectives are to evaluate preliminarily the effects of AK002 in patients with EG and/or EGE by comparing AK002 to placebo treatment for the following parameters:

1) Changes in symptoms of EG and EGE in a Patient Reported Outcome (PRO) questionnaire.
2) Change in [redacted].
3) Compare responders between AK002 and placebo; a responder is a patient who exhibits a >30% reduction in CSI (abdominal pain, nausea, and diarrhea) and a >75% reduction in mucosal eosinophils.

### 4.3 Exploratory Objectives

The exploratory objectives are to evaluate the effect of AK002 in patients with EG and/or EGE by comparing AK002 to placebo treatment for the following parameters:

1) Number of [redacted] in patients with [redacted]
2) [redacted] before and after treatment.
3) Change in [redacted], respectively.
4) Change in [redacted].
5) Change in [redacted] and [redacted].
6) Scoring of [redacted] using the [redacted].

### 4.4 Safety Objectives

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

## 5. Study Design

### 5.1 Study Overview

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability, and pharmacodynamic effect of AK002 in patients with EG and/or EGE.

Screening data will be reviewed to determine patient eligibility. Subjects with EG and/or EGE who meet all inclusion criteria and none of the exclusion criteria are eligible to be enrolled into the study. Subjects who do not meet all eligibility criteria at screening, or who qualify but are not enrolled, may be assigned a new Patient ID number and re-screened once. Subjects re-screened within 30 days of signing the initial consent will not need to sign a new ICF providing there have been no changes to the ICF. Subjects with screening EGD biopsy results <3 months prior to rescreening do not need to undergo repeat procedures.

The study is designed as follows:

- A 14 to 35-day screening period with baseline evaluations for study eligibility, including baseline active symptoms of disease (gathered by PRO completed during screening) and Esophago-Gastro-Duodenoscopy (EGD) with biopsy.
- If subjects meet histology and symptom eligibility criteria, they will receive 4 doses of AK002 or placebo by IV infusion on Days 1, 29 (±3), 57 (±3), and 85 (±3).
- A repeat EGD with biopsy will be performed on Day 99 (±3).
- Subjects will be followed for 56 (±3) days after the last dose. Follow-up visits will occur on Days 113 (±3) and 141 (±3).
- If the absolute lymphocyte and/or eosinophil counts have not recovered by Day 141, the follow-up period will be extended, and subjects will be followed until the counts have recovered. During the extended follow-up period, subjects will return to the site every 28 days (±3) for a follow-up safety visit.

Total study duration will be up to approximately 23–25 weeks (study duration could be extended as described above, if the absolute lymphocyte and/or eosinophil counts have not recovered).

Pre-study medications and pre-existing dietary restrictions should remain unchanged throughout the study. Subjects will undergo a standardized baseline evaluation of eating habits, food habits/restrictions and food avoidance behaviors and will be asked to maintain similar habits and restrictions throughout the study.

Subjects who complete through Day 113 may have the option to receive AK002 in a separate open-label extension study, if all eligibility criteria for the extension study are satisfied. Subjects who enroll in the AK002-003X extension study will begin extension study dosing immediately after completing the Day 113 visit of the AK002-003 protocol. Subjects will not complete the Day 141 procedures or extended follow-up under the AK002-003 protocol. Open-label dosing and follow-up including any extended follow-up required to monitor the recovery of lymphocytes and eosinophils will occur under the AK002-003X extension protocol.

### 5.2 Schedule of Events

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

**Table 1 Schedule of Assessments**

| | Visits | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening (Up to 5 Weeks) | Treatment Period (12 Weeks) | | | | | | Post-Treatment Follow-up Period (8 Weeks) | | | Extended Follow-up (if needed) |
| Assessments | Baseline[1] | Day 1[1] | Day 4 (±1 day) | Day 15 (±2 days) | Day 29 (±3 days) | Day 57 (±3 days) | Day 85 (±3 days) | Day 99 (±3 days) | Day 113 (±3 days) | Day 141 (±3 days) or ET[30] | Every 28 Days[32] (±3 days) |
| Informed consent | X | | | | | | | | | | |
| Demographics | X | | | | | | | | | | |
| Medical History | X | X | | | | | | | | | |
| Prior/concomitant Medications | X | X | | X | X | X | X | X | X | X | |
| Body weight and height[2] | X | X | | X | X | X | X | | X | X | |
| Vital Signs[3] | X | X | | X | X | X | X | | X | X | |
| 12-lead ECG[4] | X | | | | | | | | | | |
| Complete Physical Examination[5] | X | | | | | | | | | | |
| Baseline Diet Assessment[6] | X | | | | | | | | | | |
| Baseline Diet Compliance[7] | | X | | X | X | X | X | X | X | X | |
| Stool for Ova and Parasite[8, 12] | X | | | | | | | | | | |
| ePRO Activation and Training[9] | X | | | | | | | | | | |
| ePRO Questionnaire[10] | <----------Perform DAILY from Screening through Day 141 or 28 days after last dose if ET----------> | | | | | | | | | | |
| [redacted] | X | X (pre-dose) | | | X (pre-dose) | X (pre-dose) | X (pre-dose) | | X | X | |
| EGD with Biopsy[12, 13] | X | | | | | | | X | | | |
| [redacted] | X | | | | | | | X | | | |
| Serum Pregnancy test & FSH[12, 15] | X | | | | | | | | | | |
| Urine Pregnancy test[16] | | X (pre-dose) | | | X (pre-dose) | X (pre-dose) | X (pre-dose) | | | X | |
| Eligibility Assessment | X | X | | | | | | | | | |
| Stratification and Randomization[17] | | X (pre-dose) | | | | | | | | | |
| Access IRT-enter PID and subject weight | | X (pre-dose) | | | X (pre-dose) | X (pre-dose) | X (pre-dose) | | | | |
| Access IRT for first subject screened to trigger first IP shipment | X | | | | | | | | | | |

**Table 1 Schedule of Assessments cont.**

| | Visits | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening (Up to 5 Weeks) | Treatment Period (12 Weeks) | | | | | | Post-Treatment Follow-up Period (8 Weeks) | | | Extended Follow-up (if needed) |
| Assessments | Baseline[1] | Day 1[1] | Day 4 (±1 day) | Day 15 (±2 days) | Day 29 (±3 days) | Day 57 (±3 days) | Day 85 (±3 days) | Day 99 (±3 days) | Day 113 (±3 days) | Day 141 (±3 days) or ET[30] | Every 28 Days[32] (±3 days) |
| Premedication with cetirizine and acetaminophen or approved alternative[18] | | X (pre-dose) | | | X (pre-dose) | X (pre-dose) | X (pre-dose) | | | | |
| Study drug administration[19] | | X | | | X | X | X | | | | |
| Symptom-directed Physical Exam[20] | | X | | X | X | X | X | | X | X | |
| CBC with differential[12, 21] | X | X | X | X | X | X | X | X | X | X | X |
| Chemistry[12, 22] | X | X (pre-dose) | | X | X (pre-dose) | X (pre-dose) | X (pre-dose) | | X | X | |
| Urinalysis[12, 23] | X | X (pre-dose) | | | X (pre-dose) | X (pre-dose) | X (pre-dose) | | X | X | |
| Serology[12, 24] | X | | | | | | | | | | |
| Blood for exploratory safety analysis (if indicated)[12, 25] | | X | | | X | X | X | | | | |
| Blood for histamine and tryptase (if indicated)[12, 25] | | X | | | X | X | X | | | | |
| Blood for PK and storage[12, 26] | X | | | X | X (pre-dose) | X (pre-dose) | X (pre-dose) | | X | X | |
| Blood for Exploratory Analysis[12, 27] | | X (pre-dose) | | | X (pre-dose) | | X (pre-dose) | | | X | |
| Blood for ADA[12, 28] | X | | | X | X (pre-dose) | X (pre-dose) | X (pre-dose) | | | X | |
| Blood for Total Serum IgE[13, 29] | | X (pre-dose) | | | | | | | | X | |
| Non-serious Adverse Events | | X | | X | X | X | X | X | X | X | |
| Adverse Events of Special Interest | | X | | X | X | X | X | X | X | X | X |
| Serious Adverse Events[31] | X | X | | X | X | X | X | X | X | X | X |
| Begin AK002-003X extension study (if applicable)[33] | | | | | | | | | X | | |

ADA: Anti-AK002 antibody
CBC: Complete blood count
ECG: Electrocardiogram
ET: Early Termination
FSH: Follicle-stimulating hormone

**Table 1 Notes**

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

2) At screening, height (in cm) and weight (in kg) will be recorded. Body weight will also be measured on Days 1,15, 29, 57, 85, and on follow-up Days 113 and 141 or ET.

3) Vital signs will be measured at screening, Days 15, 99, 113, 141 or ET and on all dosing days pre-dose, 15 minutes (±5 minutes) after the start of study drug infusion, immediately following the end of infusion on treatment days (+5 minutes), 1 hour (±15 minutes) into the post-infusion observation period and just prior to discharge. Vital signs including systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate will be measured after the subject has been at rest for >5 minutes and before any blood draw.

4) An ECG will be obtained at screening before any blood is drawn and after the subject has been in the supine 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 Baseline Diet Assessment will be performed using standardized questions. Eating patterns, food avoidance behaviors, and allergies will be captured.

7) A Baseline Diet Compliance check will be performed and any variances from the baseline diet documented. Subjects should try to maintain the baseline diet as much as possible throughout the study.

8) Fecal collection kits for Ova and Parasite test will be provided to subjects at screening. Collection kits should be returned to the clinical site within 1 day of collection.

9) Activate EG/EGE PRO questionnaire and provide subject with unique username and password. EG/EGE PRO questionnaire should be activated for all subjects. Subjects with concomitant history of atopic asthma, atopic dermatitis and/or eosinophilic esophagitis will receive an extra question, about each, as appropriate.

10) EG/EGE PRO should be completed around the same time each day. Prior to enrollment, the EG/EGE PRO weekly averages over the screening period will be calculated and used to assess eligibility and establish the baseline severity of symptoms.

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

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

13) See Appendix 5 for biopsy assessments. The post-treatment endoscopy (EGD) and biopsy assessments will be performed on Day 99 (±3) and biopsy results will be blinded.

14) To be performed during the conduct of the EGD during the screening period and on D99.

15) Blood for serum pregnancy and FSH will be collected on screening, for subjects of childbearing ability or to show post-menopausal status.

16) Urine for urine pregnancy test will be collected pre-dose on all infusion days and at EOS. Test kits will be supplied by the central lab. Tests will be completed on site and evaluated prior to infusion(s).

17) Stratification based on highest weekly symptom average recorded (group of 3.0–4.9 or 5.0–10.0). Randomization and stratification will occur through Cenduit IRT.

18) Premedication required prior to first and second infusions and at the Investigator's discretion for third and fourth infusions, depending on tolerance of prior infusions.

19) Study drug will be administered as a single peripheral IV infusion over at least 5 hours on study Day 1 and at least 4 hours on Day 29 (±3 days) and Day 57 (±3 days). The infusion may be shortened to 3–5 hours for Day 85 (±3 days). Please refer to the Pharmacy Manual for detailed instructions on study drug preparations, administration, and infusion rates. Infusion must be completed within 8 hours of preparation of study drug.

20) 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.

21) Blood for CBC with differential, including absolute [redacted] and basophil counts, will be obtained just prior to each infusion, 1 hour after the end of each infusion, 4 hours after the end of infusion 1, as well as during the screening period and on Days 4, 15, 99, 113, and 141 or ET and Extended Follow-Up, if applicable. All differential blood counts from Day 1 (post-dose) and prior to Day 141 or Early Termination will be blinded to the Sponsor and the site. An unscheduled CBC may be collected at the request of the unblinded safety monitor. Differential blood counts will not be blinded at the Day 141/ET visit and these results will be used by the site to determine if the subject needs to enter the Extended Follow-Up period.

22) Blood for chemistry will be obtained pre-dose on dosing Days 1, 29, 57, and 85, as well as during the screening period and on Day 15, Day 113, and Day 141 or ET.

23) Urine for standard urinalysis will be obtained pre-dose on dosing Days 1, 29, 57, and 85, as well as during the screening period and on Day 113 and Day 141 or ET.

24) Serology will include HBsAg, hepatitis C antibody, anti-HBc, and HIV.

25) If an Infusion-related reaction causes an infusion interruption or cessation a sample of blood should be obtained for exploratory safety analysis within 1–2 hours of the onset of the symptoms. A sample of blood should be obtained for testing of histamine and tryptase levels within 1–2 hours, if anaphylaxis is suspected.

26) Blood for PK should be obtained pre-dose on dosing Days 29, 57, and 85, as well as during screening and on Days 15, 113, and 141 or ET.

27) Blood samples for exploratory analysis will be collected pre-dose on Days 1, 29, and 85 and also on Day 141 or ET.

28) Blood samples for ADA will be collected during the screening period, on Days 15, 29, 57, 85 and Day 141 or ET and anytime an immunogenicity-related AE occurs.

29) Blood samples for Total Serum IgE will be collected on Day 1 and on Day 141 or ET.

30) The ET Visit should be conducted 28 (±3) days after the last dose of study drug or prior to this, if necessary, to ensure compliance with the visit. If early termination occurs more than 28 days after the last dose of study drug, then perform the ET visit as soon as possible. The procedures listed under the final follow-up visit will be conducted unless directed otherwise by the Medical Monitor.

31) The reporting of Serious Adverse Events 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 other SAEs and Adverse Events that are not SAEs will begin at the time of first infusion of study drug.

32) Extended follow-up, if needed, every 28 days (±3 days) until eosinophil and/or lymphocyte counts have recovered.

33) Subjects who sign the informed consent for the AK002-003X extension study will complete the procedures for Day 113 and then immediately begin open-label dosing in the extension study if eligible. Subjects will not complete the Day 141 procedures or extended follow-up under the AK002-003 protocol. Open-label dosing and follow-up including any extended follow-up required to monitor the recovery of lymphocytes and eosinophils will occur under the AK002-003X extension protocol.

# 6. Criteria for Evaluation

## 6.1 Safety Endpoints

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

- Physical examination (Section 11.3.2, 11.3.5)
- Changes in vital signs (Section 11.3.7)
- Hematology (Section 11.4.1)
- Changes in concomitant medication use due to AEs (Section 11.3.1)
- Blood chemistry (Section 11.5)
- Urinalysis (Section 11.5.2)
- ADA (Section 11.5.4)
- AEs (Section 13) include severity, withdrawals due to AEs, and other safety parameters

## 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 day, pre-dose on Days 29, 57, and 85, and additionally on Days 15, 113, and Day 141 (or ET).

Blood (serum) will be collected for assessment of ADA using a validated assay method. ADA blood samples will be obtained on screening day, pre-dose on Days 29, 57, and 85, and additionally on Days 15 and 141 (or ET). AK002 concentrations in serum will be used to calculate AK002 exposure.

## 6.3 Efficacy Endpoints

<u>Primary Endpoint</u>

- Percent change from baseline in the number of eosinophils per HPF in gastric or duodenal mucosa. For subjects who provide both gastric and duodenal biopsies, the calculation will be based on the average count of the highest readings from the combined pool of gastric and duodenal mucosa.

<u>Secondary Endpoints</u>

- Changes from baseline in the weekly averages of symptoms as measured by the PRO Questionnaire total and item daily scores for 8 different symptoms:

  - Abdominal pain intensity
  - Nausea intensity
  - Vomiting intensity
  - Vomiting frequency
  - Diarrhea intensity
  - Diarrhea frequency
  - Early satiety intensity
  - Loss of appetite intensity
  - Bloating intensity
  - Abdominal cramping intensity
- Change from baseline in the number of eosinophils in gastric mucosa in patients with EG.
- Change from baseline in the number of eosinophils in duodenal mucosa in patients with EGE.
- Compare responders between AK002 and placebo; a responder is a patient who exhibits a >30% reduction in CSI (abdominal pain, nausea, and diarrhea) and a >75% reduction in mucosal eosinophils.
- Change in [redacted].

### 6.4 Exploratory Endpoints

- Change from baseline in the number of [redacted] in patients with [redacted]
- [redacted] before and after treatment.
- Change in [redacted], respectively.
- Changes in [redacted].
- Change in [redacted] and [redacted].
- Scoring of [redacted] using the [redacted].

# 7. Patient Selection

## 7.1 Number of Patients

A total of approximately 60 subjects will be dosed in the study in which 20 subjects will receive AK002 at a dose of 0.3 mg/kg for the first dose followed by 1 mg/kg for 3 subsequent doses, 20 subjects will receive AK002 at a dose of 0.3 mg/kg for the first dose, followed by 1 mg/kg for the second dose and 3 mg/kg for 2 subsequent doses, and 20 subjects will receive placebo, in a randomized, double-blind fashion.

## 7.2 Study Population

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

## 7.3 Inclusion Criteria

Patients with a diagnosis of EG or EGE are eligible for enrollment into the study if all of the following criteria are met:

1) Male or female aged ≥18 and ≤80 years at the time of signing ICF.

2) Average weekly score of ≥3 (on a scale from 0–10) recorded for either abdominal pain, diarrhea and/or nausea on the PRO questionnaire during at least 2 weeks or 2 of the last 3 weeks of PRO collection. A minimum of four questionnaires must be completed each qualifying week.

3) Eosinophilia of the gastric mucosa ≥30 eosinophils/HPF in 5 HPFs and/or eosinophilia of the duodenal mucosa ≥30 eosinophils/HPF in 3 HPFs from the EGD performed during the screening period, without any other cause for the gastric eosinophilia (e.g., parasitic or other infection or malignancy).

4) Subjects must have failed or not be adequately controlled on standard-of-care treatments for EG or EGE symptoms (which could include PPIs, systemic or topical corticosteroids, and/or diet, among others).

5) If on other treatments for EG, EGE, or EoE at enrollment, stable dose for at least 5 half-lives prior to screening and willingness to continue on that dose for the duration of the study.

6) If subject is on pre-existing dietary restrictions, willingness to maintain dietary restrictions throughout the study, as much as possible.

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

8) Female subjects must be either post-menopausal for at least 1 year with FSH level >40 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 subjects 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 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) Known hypersensitivity to any constituent of the study drug.
2) Diagnosis of celiac disease or active *H. pylori* infection as determined by screening EGD or a history of celiac disease diagnosed by prior EGD.
3) Presence of abnormal laboratory values considered by the Investigator to be clinically significant.
4) Grade 2 or higher lymphopenia ($<0.8 \times 10^9$/L lymphocytes).
5) Any disease or condition (medical or surgical) or cardiac abnormality, which, in the opinion of the Investigator, would place the subject at increased risk.
6) History of malignancy; except carcinoma in situ, early stage prostate cancer, or non-melanoma skin cancers. However, cancers that have been in remission for more than 5 years and are considered cured, can be enrolled (with the exception of breast cancer). All history of malignancy (including diagnosis, dates, and compliance with cancer screening recommendations) must be documented and certified by the Investigator, along with the statement that in their clinical judgment the tissue eosinophilia is attributable to EGID, rather than recurrence of malignancy.
7) Treatment with chemotherapy or radiotherapy in the preceding 6 months.
8) Treatment for a clinically significant helminthic parasitic infection within 6 months of screening and/or a positive helminthic test at screening.

9) Use of any medications that may interfere with the study such as immunosuppressive or immunomodulatory drugs (including azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, tacrolimus, anti-TNF, anti-IL-5, anti-IL-5 receptor, dupilumab, anti-IgE antibodies, omalizumab) or systemic corticosteroids with a daily dose >10 mg of prednisone or equivalent, during 5 half-lives prior to screening or during the screening period, except for omalizumab taken for asthma and/or urticaria when their asthma and/or urticaria cannot be controlled on other medications. If on omalizumab, the dose must have been stable for at least 4 weeks prior to screening.

10) 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 of the study drug administration.

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

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

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

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

15) Diagnosis of Hypereosinophilic Syndrome (HES), based on standard criteria (blood eosinophils >1500/μL with involvement of either the heart, nervous system, and/or bone marrow).

## 8. 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 (eCRFs) for 30 days prior to the screening visit.

Any medication must have been stopped as required in Exclusion Criteria. Subjects should be advised against taking any new medication, both prescribed and over the counter, without consulting the Investigator, unless the new medication is required for emergency use. Immediately prior to the first infusion, the study site personnel should ensure that the subject 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 IRRs or AEs must also be documented.

### 8.1 Prohibited Medications

Any medications that may interfere with the study such as immunosuppressive or immunomodulatory drugs (including azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, tacrolimus, anti-TNF, anti-IL-5, anti-IL-5 receptor, dupilumab, anti-IgE antibodies, omalizumab) or systemic corticosteroids with a daily dose >10 mg of prednisone or equivalent. The use of omalizumab by asthma and/or urticaria patients for asthma and/or urticaria that cannot be controlled on other medications is allowed, as long as the dose has been stable for at least 4 weeks prior to screening, and expected to remain stable throughout the study.

### 8.2 Allowed Medications

Medications (other than those that are prohibited [Section 8.1]), such as antihistamines, leukotriene antagonist and sodium cromolyn, are allowed during the study and, unless required due to unforeseen medical necessity, doses are to remain stable. All medication use will be documented in the eCRF.

## 9. Study Treatment

### 9.1 Formulation of Test Product 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 [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 [redacted], pH 6.0, in sterile water for injection.

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

### 9.2 Study Drug Packaging and Labeling

AK002 drug product is supplied as a sterile liquid in a single-use 10R glass vial with a fill volume of approximately 10.6 mL. 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 subject ID and preparation date.

This tear-off label should be applied to the IP Dose Calculation and Preparation Worksheet and maintained with the UNBLINDED source documents, away from all blinded staff.

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

### 9.3 Supply of Study Drug to the Investigational Site

The Sponsor (or designee) will ship study drug to the investigational sites. The initial study drug shipment will be shipped after all required regulatory documentation and approvals have been received by the Sponsor, contract has been executed, and the first screened subject 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

Subjects will be randomly assigned through the IRT system to dosing groups of 1 mg/kg AK002 (first dose at 0.3 mg/kg), 3 mg/kg AK002 (first dose at 0.3 mg/kg, second dose at 1 mg/kg), or placebo. The exact dose will be calculated prior to each infusion and based on current subject 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), and 85 (±3).

### 9.5 Preparation of Study Drug

An unblinded study pharmacist or designee will prepare the study drug for each infusion. This unblinded pharmacist/designee must not participate in any study-related activities where blinding is required. Based on subject weight obtained the day of dosing, the designated study pharmacist will prepare the appropriate dilution of AK002 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.

The infusion must be completed within 8 hours of preparation.

### 9.6 Study Drug Administration

Specific instructions on administration and supplies required for administration are detailed in the Pharmacy Manual. In general, study drug will be infused through a peripheral vein intravenous (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 5 hours on Study Day 1, over at least 4 hours on Study Days 29 and 57, and over at least 3 hours on Study Day 85. If the infusion is slowed or interrupted, the time may be extended longer than 5 hours, as long as it does not exceed 8 hours.

For the first and second infusions of study drug, subjects will be premedicated with cetirizine and acetaminophen, or an alternative premedication approved by the Allakos Medical Monitor. If the first 2 infusions are well tolerated, it is at the Investigator's discretion whether to premedicate for the third and fourth infusions.

The IV infusion may be interrupted, and/or the rate may be reduced if a subject has an infusion-related reaction (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 subject experiencing a serious adverse event during the course of the infusion.

If the subject experiences an IRR that causes an interruption or cessation of the study drug infusion, an 11 mL blood sample should be collected within 1–2 hours of the onset of symptoms, for exploratory safety analysis. If the subject experiences signs or symptoms of anaphylaxis, a blood sample should be collected within 1–2 hours of the onset of symptoms for the analysis of histamine and tryptase levels.

The subject will be observed for 4 hours after the end of the first and second infusions, and if no issues are noted, will be observed for 2–4 hours for subsequent infusions, as per Investigator discretion.

* 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.

### 9.7 Study Drug Storage

AK002 will be stored by the study sites at 2°C to 8°C under lock at the designated pharmacy. Access will be restricted to designated pharmacy staff. The NaCl 0.9% will be stored at ambient temperature, per manufacturer's requirements. All study drug and NaCl will be stored in an area that is temperature controlled and monitored. If the temperature of study drug storage in the clinic/pharmacy exceeds or falls below this range, this will be reported to the Sponsor or

designee and captured as a deviation. The Sponsor will notify the site if the study drug is to be quarantined or can be used.

### 9.8 Study Drug Accountability

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

All study drug accountability logs will be considered UNBLINDING and must be maintained under secure storage locations, away from any blinded study activity.

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

### 10.1 Subject Numbering

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

- The first 3 digits designate the study number. For this study, the number is 203.
- The second 3 digits designate the site number.
- The last 3 digits designate the order of consent at the site (the first subject who provides consent is 001, the second subject is 002, and so forth).

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

### 10.2 Stratification and Randomization

To be randomized into the study, a subject must have an average weekly score of $\geq$3 (on a scale from 0–10) recorded for either abdominal pain, diarrhea and/or nausea on the PRO questionnaire during at least 2 weeks of PRO collection. A minimum of 4 questionnaires must be completed on each qualifying week. Subjects will be randomized through the Interactive Response Technology (IRT) system.

If the subject qualifies for the study after completing all of the screening procedures, on the day of first infusion (Study Day 1), the site will access the IRT system in order to randomize and stratify the subject in the study and enter the current body weight for study drug dose calculation. The site will identify the highest average weekly score for any qualifying symptom of disease recorded during the screening period in order to stratify subjects to 1 of 2 groups, namely PRO score 3–4.9 or 5.0–10.0. The IRT system will then randomly assign the subject to AK002 at a dose of 0.3 mg/kg (first dose) followed by 1 mg/kg (subsequent doses), AK002 at a dose of 0.3 mg/kg (first dose), 1 mg/kg (second dose), followed by 3 mg/kg (subsequent doses), or placebo in a double-blind fashion and will send an email to the unblinded pharmacist detailing the treatment assignment.

Twenty subjects will be randomized to treatment with AK002 at a dose of 0.3 mg/kg first dose/ 1 mg/kg subsequent doses; 20 subjects randomized to AK002 at a dose of 0.3 mg/kg first dose/ 1 mg/kg second dose/3 mg/kg subsequent doses; and 20 subjects randomized to placebo.

A subject is considered enrolled in the trial when the subject is randomized.

For subsequent infusions on Days 29, 57, and 85, the coordinator will access the IRT on the day of infusion and enter the PID as well as the subject's body weight, and the system will assign the subject the dose according to their randomization number. The unblinded pharmacist will then receive an email detailing the kit number to prepare.

Prior to each infusion, the Investigator or designee will confirm the PID recorded on the IV bag provided by the unblinded pharmacist matches the subject. The subject identification should be confirmed and documented by a second party prior to administering the infusion, whenever possible. Neither the treatment group nor the dose prepared (0.3, 1, or 3 mg/kg or placebo) should ever be recorded on the IV infusion bag.

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

### 10.3 Blinding

The identity of test and control treatments will not be known to Investigators, Sponsor, research staff, subjects, or the primary study monitor. Only the unblinded study pharmacist(s) and the unblinded pharmacy monitor will know the treatment assignment.

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

- Access to the randomization codes will be strictly controlled via IRT.
- Throughout the study, the blind should remain unbroken except for an emergency when knowledge of the subject's study medication is necessary for further management or if required for regulatory reporting. The Allakos Medical Monitor approves any emergency blind break, if at all possible, prior to the unblinding.
- The AK002 and placebo for infusion will be identical in appearance, once prepared by the pharmacist.
- 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 exploratory analysis, exploratory safety analysis (unless immediately required for safety issues) and any histamine/tryptase tests will not be provided to the Investigator and Sponsor until after database lock.
- After the initial infusion of study drug and prior to enrolling in the AK002-003X extension study (if applicable), Day 141 or Early Termination, results of the assessments noted below will not be provided to the Investigator and Sponsor until after database lock. The results will be reviewed on an ongoing basis by an unblinded safety monitor and escalated as appropriate.
  - Differential cell counts (including neutrophils, eosinophils, basophils, monocytes, and lymphocytes).
  - Enumeration of eosinophils and [redacted] from Day 99 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.

### 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. 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 performing an emergency breaking of the blind. Reason for unblinding, person conducting the unblinding, person(s) who know the unblinded treatment, and date/time of unblinding will be recorded.

## 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:

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

### 11.1 Dietary and Lifestyle Restrictions

Subjects 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 eCRFs at each study visit.

### 11.2 Pharmacodynamic/Efficacy-Related Procedures

#### 11.2.1 PRO Questionnaire

An electronic version of the PRO questionnaire (Appendix 1) will be completed daily every evening at approximately the same time by the subject throughout the study.

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

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

If subjects have a history of concomitant atopic dermatitis, atopic asthma, or eosinophilic esophagitis, an extra question will be populated for each relevant condition on the website for the subject to complete daily. A paper version of these questions (Appendix 9) is available, should the website not be accessible or the subject not have Internet access.

### 11.2.2 [redacted]

A paper version of the [redacted] (Appendix 2) will be completed by the subject at the screening visit, pre-dose on infusion on Days 1, 29, 57, and 85, and on follow-up Days 113 and 141 (or ET). This information will be entered into the EDC by the study site.

### 11.2.3 Esophago-Gastro-Duodenoscopy with Biopsy

An Esophago-Gastro-Duodenoscopy (EGD) with biopsy will be performed during the screening period and on Day 99 (±3 days). Biopsy samples will be collected according to standardized instructions and will be sent to the Central Lab (or designee) for fixing and staining. A blinded Central reader will report, among other things, maximum number of eosinophils per HPF, maximum number of tryptase-positive mast cells per HPF, and gastric biopsies will be graded using the Sydney System on inflammation, metaplasia, atrophy, and reactive gastropathy. The Marsh Scale Classification will be used to grade duodenal samples.

During the conduct of the EGD, an attending practitioner will assess and grade various aspects of the GI tract, according to the [redacted] (Appendix 7).

Day 99 EGD results will not be provided to the Investigator and Sponsor until after database lock. An unblinded 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 subject's eligibility can be verified.

- Inclusion #3: Eosinophilia of the gastric mucosae ≥30 eosinophils/HPF in 5 HPFs or of the duodenal mucosa ≥30 eosinophils/HPF in 3 HPFs from the EGD performed during the screening period, without any other cause for the gastric/duodenal eosinophilia.
- Exclusion #2: Diagnosis of celiac disease or active *H. pylori** infection as determined by screening EGD or a history or celiac disease diagnosed by prior EGD.
    - * A diagnosis of active *H. pylori* at screening may be treated with standard therapies and as long as confirmed negative prior to enrollment and symptoms remain stable, the subject may be randomized into the study.

### 11.2.4 Complete Blood Count with Differential

Blood will be obtained for complete blood count (CBC) with differential at the screening visit, as well as pre-dose and 1-hour post-dose on Days 1, 29, 57, and 85, and on follow-up Days 4, 15, 99, 113, 141 (or ET), as well as during the Extended Follow-Up period, if appropriate. On Infusion Day 1, a blood sample will also be collected 4 hours after the end of the infusion. 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, basophils).

The Day 4 blood sample may be collected on site, or the subject may be sent home with a Central lab hematology collection kit, shipping label, and laboratory requisition. If the sample is not collected on site, the subject may go to a local lab or have a visit from a home nurse to collect this sample, to be sent to the Central lab for analysis. The differential hematology results must remain blinded.

The blood differential test results (neutrophils, eosinophils, basophils, monocytes, and lymphocytes) will be blinded from the Investigator and Sponsor from post-dose Day 1 and prior to Day 141 or Early Termination, 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 unblind blinded members of the study. An unblinded 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 unblinded Safety Monitor and evaluated in real time.

Day 141 or Early Termination blood differential results will not be blinded in order to allow for confirmation of eosinophil and lymphocyte recovery and to identify those subjects that need to enter the Extended Follow-Up period.

### 11.2.5 Baseline Diet Assessment

During the screening visit the Investigator or designee will ask the subject 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 every study visit, on Days 1, 15, 29, 57, 85, 99, 113, and 141 (or ET). Whether or not the subject has maintained the baseline diet and if not, what deviations were made, should be documented in the source and the eCRF.

### 11.2.6 [redacted]

In association with the conduct of the EGD during the screening period and on Day 99 (or ET), the attending physician will assess and grade various [redacted], according to the [redacted]. See Appendix 7.

## 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 141 (or ET) will be recorded.

### 11.3.2 Complete Physical Examination

A complete physical exam will be performed by either the Investigator or a qualified Subinvestigator 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, and 85 only, weight will be calculated pre-dose 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 (UNBLINDING) that the unblinded pharmacist will maintain and document for each subject's dose calculations. Body weight should be collected on site on the day of each study drug infusion, or the day prior to each infusion.

Body weight will also be captured on Days 15, 113, and 141 or ET.

### 11.3.4 Stool Sample for Ova and Parasite

At screening, fecal collection kits will be provided to subjects for the Ova and Parasite test. Subjects 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). Historic lab results showing negative helminthic infections from 90 days prior to screening may be used to satisfy this criterion, at the discretion of the Investigator.

### 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 IRRs, will be performed by either the Investigator or a qualified Subinvestigator 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 study doctor 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 subject has been in the supine 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 subject 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 supine systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate, will be taken after the subject has been at rest for ≥5 minutes and before any blood draw (except for post-infusion for which vital signs will be obtained as described below).

On dosing days, vital signs will be measured pre-dose, 15 minutes (±5 minutes) after the start of infusion, immediately following the end of infusion (+5 minutes), 1 hour (±15 minutes) into the observation period 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 adverse events or abnormal lab values.

The site will process and ship blood and urine samples per central laboratory instructions. A central laboratory or designee will analyze blood and urine samples and provide results for the following clinical safety laboratory tests (Sections 11.4.1–11.5.6).

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

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

### 11.4.1 Complete Blood Count with Differential

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

## 11.5 Blood Chemistry Profile

Blood will be obtained for chemistry tests at screening and pre-dose on dosing Days 1, 29, 57, and 85, as well as Days 15, 113, and 141 or E/T. The blood sample will be processed and shipped in accordance with central laboratory manual and laboratory kit instructions. A central laboratory will analyze the serum sample and provide results for chemistry tests including sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, creatine kinase, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, aspartate aminotransferase (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 test will be obtained for all female subjects 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 >40 mIU/mL are not considered to be of childbearing potential. At screening, FSH will be tested on female subjects to confirm post-menopausal status. Both samples will be processed by the Central Laboratory.

On Days 1, 29, 57, and 85 (prior to each dose), and at Day 141 or ET, pre-menopausal females (screening FSH level ≤40 mIU/mL) will provide a urine sample for pregnancy (hCG) testing. The site will perform a urine pregnancy hCG test using an indicator stick from the pregnancy test kit supplied by the central laboratory. This test is to be assessed by the study staff prior to the start of each study drug infusion.

### 11.5.2 Urinalysis

Urine will be obtained for urinalysis at screening and on Days 1, 29, 57, 85, 113, and 141 (or 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 laboratory manual and lab kit instructions. A positive result, if clinically significant (and not due to previous vaccination) would exclude the subject from enrollment.

### 11.5.4 Anti-AK002 Antibodies

Blood will be collected for determination of ADA at screening, on Days 15, 29, 57, 85 and on Day 141 (or ET), and 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 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, and 85 and follow-up Days 15, 113, and 141 or ET. The serum samples will be processed and shipped frozen in accordance with the study laboratory manual and laboratory kit instructions.

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

### 11.5.6 Blood for Exploratory Analysis

Blood samples for exploratory analysis will be collected pre-dose on Days 1, 29, and 85 and also on Day 141 or ET. The serum samples will be processed and shipped frozen in accordance with the study laboratory manual and laboratory kit instructions.

### 11.5.7 Blood for Exploratory Safety Analysis, 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 the symptoms. The sample will be sent to the central lab for processing. If the subject experiences an IRR that causes an interruption or cessation of the study drug infusion a blood sample should be collected within 1–2 hours of the onset of symptoms, for exploratory safety analysis.

### 11.5.8 Additional Samples for Biomarker Sub-Study

At selected study sites, additional samples (blood, urine, and biopsy) will be collected for a sub-study to evaluate biomarkers. See Appendix 8.

## 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 first infusion.

### 12.1 Screening Period

1) Obtain written informed consent.
2) Assign the participant a Patient ID Number (PID).
3) Begin the collection of serious adverse events related to any screening activities.
4) Collect demographics and medical history.
5) Record prior and concomitant medications.
6) Determine body weight and height.
7) [redacted] to be completed by the subject.
8) Perform Baseline Diet Assessment.

9) Obtain vital signs before blood draws.

10) Perform a complete physical examination.

11) Obtain a 12-lead ECG before blood draw.

12) Collect the following samples for the central laboratory:
    a) Serum pregnancy test and FSH (if subject of childbearing potential or post-menopausal)
    b) CBC with differential
    c) Chemistry
    d) Urinalysis
    e) Blood for Anti-AK002 antibody
    f) Blood for Serology testing
    g) Blood for PK and storage

13) Provide subject a stool collection kit and ask them to return it to the site within 1 day of collection (unless subject can provide sample while on site).

14) Activate subject access to daily EG and/or EGE PRO questionnaire and instruct subject on use of the questionnaire.

15) Perform a Screening/Baseline Esophago-Gastro-Duodenoscopy (EGD) with biopsy following procedures provided by Allakos. Assess and grade [redacted] using the [redacted].

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

### 12.2 Day 1 – Day of First Infusion

1) Prior to the infusion:
    a) Assess the subject 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) [redacted]
    g) Determine body weight

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

i) Collect vital signs

j) Perform symptom-directed physical exam, as needed

k) CBC with differential

l) Chemistry

m) Urinalysis

n) Blood for Total Serum IgE

o) Blood for Exploratory analysis

p) Cetirizine 10 mg and acetaminophen 1000 mg (or approved alternative) will be administered as premedication approximately 1 hour before dosing

2) Prior to randomizing the subject in the IRT system, the site will identify the highest weekly average score recorded for any of the following symptoms of disease during at least 2 weeks of PROs: abdominal pain, nausea, and/or diarrhea. The study coordinator or designee will enter the highest average qualifying score into the IRT on Study Day 1 to stratify the subject, as well as body weight and PID.

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

4) The unblinded study pharmacist will prepare study drug using the weight obtained at the visit. The final combined volume of the IV bag of study drug + 0.9% NaCl will be **120** mL. Note: **100 mL** of the calculated dose of study drug will be administered to the subject. The extra 20 mL is to be used to prime the IV infusion line during the preparation of the IV line at the bedside or to be left over in the infusion bag.

5) Infusion of Study Drug:

a) Infuse 100 mL of study drug over at least 5 hours using an infusion pump. See Pharmacy Manual for Infusion Rates. Record the start and stop times of the infusion including any times the infusion is interrupted.

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

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

6) Post-infusion:
   a) Collect vital signs immediately following (+5 minutes) the end of infusion.
   b) Collect CBC with differential 1 hour (±15 minutes) after the end of the infusion. Collect vital signs 1 hour (±15 minutes) after the end of the infusion, as well as immediately prior to discharge home.
   c) Collect CBC with differential 4 hours (±15 minutes) after the end of the infusion.
   d) Observe the patient for at least 4 hours after the end of infusion.

### 12.3 Day 4 (±1)

1) CBC with differential.

### 12.4 Day 15 (±2)

1) Assess the subject for AEs and SAEs.
2) Document any changes to concomitant medications.
3) Document any changes to baseline diet.
4) Collect vital signs.
5) Perform symptom-directed PE, as needed.
6) CBC with differential.
7) Chemistry.
8) Blood for Anti-AK002 antibody.
9) Blood for PK and storage.

### 12.5 Day 29 (±3) – Day of Second Infusion

1) Prior to the infusion:
   a) Assess the subject for AEs and SAEs
   b) Document any changes to concomitant medications
   c) Document any changes to baseline diet
   d) [redacted]
   e) Determine body weight
   f) Perform urine pregnancy test (if subject is of childbearing potential)
   g) Collect vital signs

h) Perform symptom-directed physical exam, as needed

i) CBC with differential

j) Chemistry

k) Urinalysis

l) Blood for PK and storage

m) Blood for ADA

n) Blood for Exploratory analysis

o) Cetirizine 10 mg and acetaminophen 1000 mg or approved alternative will be administered as premedication approximately 1 hour before dosing.

p) The IRT will be accessed, and the subject's PID and body weight will be entered. Only the unblinded study pharmacist will receive the treatment assignment and kit number for the subject.

2) The unblinded study pharmacist will prepare study drug using the current weight obtained.

3) Infusion of Study Drug:

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

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

c) If the subject experiences an IRR that causes an interruption or cessation of the study drug infusion a blood sample should be collected within 1–2 hours of the onset of symptoms, for exploratory safety analysis. 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 immediately following (+5 minutes) the end of infusion.

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

c) Observe the subject for 4 hours after the end of the infusion.

d) Collect vital signs 1 hour (±15 minutes) after the end of the infusion, as well as immediately prior to discharge home.

### 12.6 Day 57 (±3) – Day of Third Infusion

1) Prior to the infusion:
   a) Assess the subject for AEs and SAEs.
   b) Document any changes to concomitant medications.
   c) Document any changes to baseline diet.
   d) [redacted].
   e) Determine body weight.
   f) Perform urine pregnancy test (if subject is of childbearing potential).
   g) Collect vital signs.
   h) Perform symptom-directed PE, as needed.
   i) CBC with differential.
   j) Chemistry.
   k) Urinalysis.
   l) Blood for PK and storage.
   m) Blood for ADA.
   n) Cetirizine 10 mg and acetaminophen 1000 mg or approved alternative may be administered as premedication approximately 1 hour before dosing, at the discretion of the Investigator or Sub-investigator and depending on tolerance to prior infusions.
2) The IRT will be accessed, and the subject's PID and weight will be entered. Only the unblinded study pharmacist will receive the treatment assignment for the subject.
3) The unblinded study pharmacist will prepare study drug using the weight obtained at the visit.
4) Infusion of Study Drug:
   a) Infuse 100 mL of study drug over at least 4 hours using an infusion pump. See Pharmacy Manual for Infusion Rates. Record the start and stop times of the infusion including any times the infusion is interrupted.
   b) Collect vital signs 15 (± 5) minutes after the start of infusion.
   c) If the subject experiences an IRR that causes an interruption or cessation of the study drug infusion a blood sample should be collected within 1–2 hours of the onset of symptoms, for exploratory safety analysis. 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.

5) Post-infusion:

   a) Collect vital signs immediately following (+5 minutes) the end of infusion.

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

   c) Observe the subject for 2–4 hours after the end of the infusion, at the Investigator's discretion and depending on tolerance to prior infusions.

   d) Collect vital signs 1 hour (±15 minutes) after the end of the infusion, as well as immediately prior to discharge home.

### 12.7 Day 85 (±3) – Day of Fourth Infusion

1) Prior to the infusion:

   a) Assess the subject for AEs and SAEs.

   b) Document any changes to concomitant medications.

   c) Document any changes to baseline diet

   d) [redacted].

   e) Determine body weight.

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

   g) Collect vital signs.

   h) Perform symptom-directed PE, as needed.

   i) CBC with differential.

   j) Chemistry.

   k) Urinalysis.

   l) Blood for PK and storage.

   m) Blood for ADA.

   n) Blood for Exploratory analysis.

   o) Cetirizine 10 mg and acetaminophen 1000 mg or approved alternative may be administered as premedication approximately 1 hour before dosing, at the discretion of the Investigator or Subinvestigator and depending on tolerance to prior infusions.

2) The IRT will be accessed, and the subject's PID and body weight will be entered. Only the unblinded study pharmacist will receive the treatment assignment and kit number for the subject.

3) The unblinded study pharmacist will prepare study drug using the current weight obtained.

4) Infusion of Study Drug:

   a) Infuse 100 mL of study drug over 3–5 hours using an infusion pump. See Pharmacy Manual for Infusion Rates. Record the start and stop times of the infusion including any times the infusion is interrupted.

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

5) Post-infusion:

   a) Collect vital signs immediately following (+5 minutes) the end of infusion.

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

   c) Observe the subject for 2–4 hours after the end of the infusion, at the Investigator's discretion and depending on tolerance to prior infusions.

   d) Collect vital signs 1 hour (±15 minutes) after the end of the infusion, as well as immediately prior to discharge home.

### 12.8 Day 99 (±3)

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

2) Collect AEs, SAEs, changes in concomitant meds, and changes in baseline diet. Collect all concomitant meds provided to the subject during the EGD.

3) CBC with differential.

4) Perform Esophago-Gastro-Duodenoscopy (EGD) with biopsy following procedures provided by Allakos and all EGD facility SOPs. Assess and grade the [redacted] using the [redacted].

### 12.9 Day 113 (±3)

1) Assess the subject for AEs and SAEs.

2) Document any changes to concomitant medications.

3) Document any changes to baseline diet.

4) [redacted].

5) Determine body weight.

6) Collect vital signs.

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

8) CBC with differential.

9) Chemistry.

10) Urinalysis.

11) Blood for PK and storage.

12) Subjects who enroll in the AK002-003X extension study will begin extension study dosing immediately after completing the Day 113 visit of the AK002-003 protocol. Subjects will not complete the Day 141 procedures or extended follow-up under the AK002-003 protocol. Open-label dosing and follow-up including any extended follow-up required to monitor the recovery of lymphocytes and eosinophils will occur under the AK002-003X extension protocol.

### 12.10 Day 141 (±3) Post-Treatment Follow-Up or Early Termination*

1) Assess the subject for AEs and SAEs.

2) Document any changes to concomitant medications.

3) Document any changes to baseline diet.

4) [redacted].

5) Determine body weight.

6) Collect vital signs.

7) Perform symptom-directed PE, as needed.

8) Urinalysis.

9) Urine pregnancy test (if subject is of childbearing potential).

10) CBC with differential.

*Note:* The absolute lymphocyte and eosinophil counts must recover for this to be the final follow-up visit. Subjects whose eosinophils and lymphocytes do not recover must enter Extended Follow-Up (see below).

11) Chemistry.

12) Blood for ADA.

13) Blood for PK and storage.

14) Blood for Exploratory analysis.

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

### 12.11 Extended Follow-Up

Subjects must return to the site every 28 (±3) days until the absolute lymphocyte and eosinophil counts recover. Data collected during Extended Follow-Up will be limited to:

1) CBC with differential

2) Adverse Events of Special Interest

3) Serious Adverse Events

## 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 one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

Examples of an AE include:

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

The following examples are not considered AEs:

- Medical or surgical procedure, although the condition leading to the procedure is usually an AE.
- Anticipated day-to-day fluctuations of preexisting medical conditions (including laboratory values) as long as significant worsening from baseline does not occur.

- Signs or symptoms of the disorder being studied, unless they become more severe or occur with a greater frequency than occurring at baseline.

All AEs, whether elicited by questions from study staff, volunteered, or noted on physical examination/laboratory testing, and regardless of causality or severity, will be assessed and recorded in the eCRF beginning after first administration of study drug and ending at Day 113 if enrolling in the AK002-003X extension study, or Day 141 (±3 days) or the ET visit unless directed otherwise by Allakos.

### 13.2 Serious Adverse Events

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

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

SAEs will be assessed and recorded after the first administration of study drug and ending at Day 113 if enrolling in the AK002-003X extension study, or Day 141 (±3 days) or the ET visit or the end of the Extended Follow-Up period if applicable, unless the SAE is related to a screening procedure, in which case it will be captured from the date of informed consent.

### 13.3 Adverse Events of Special Interest

Adverse Events of Special Interest (AESIs) for this trial include:

- Malignancies confirmed by histopathological report. (Mast cells and eosinophils are part of the normal immune response, by decreasing their function, AK002 could theoretically increase the risk of malignancy)
- Parasitic infections confirmed by positive clinical laboratory test. (Eosinophils are especially active in protecting the body from parasitic infections and decreasing their function could theoretically increase the risk of parasitic and opportunistic infections)

- Opportunistic infections (infections known to be more severe or occur more frequently in immunosuppressed populations) as confirmed by positive clinical laboratory test.
- Infusion-related reactions and hypersensitivity reactions, including anaphylaxis.

Beginning from the time of first study drug infusion and ending at Day 113 if enrolling in the AK002-003X extension study or Day 141 (±3 days) or the ET visit or the end of the Extended Follow-Up period, if applicable, any new AESI (or new information related to a previously reported AESI) must be recorded in the AE eCRF and designated as an "adverse event of special interest."

### 13.4 Infusion-Related Reactions

All Adverse Events, 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 one IRR.

Common symptoms of IRRs include (but are not exclusive to):

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

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

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

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

### 13.6 Evaluating Adverse Events and Serious Adverse Events

#### 13.6.1 Establishing Diagnosis

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

The Investigator (or qualified Subinvestigator) must assign the following AE attributes listed below and is responsible for ensuring their capture in the source documentation.

#### 13.6.2 Assessment of Intensity

The Investigator will use their clinical judgment as well as the guidelines laid out in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (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 ADL. |
| 3 | Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. |
| 4 | Life-threatening consequences, urgent intervention indicated. |
| 5 | Death related to AE. |

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

The term "severe" is a measure of intensity, and a severe Adverse Event (AE) is not necessarily a Serious Adverse Event (SAE).

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

### 13.6.3 Assessment of Causality to Study Drug

The Investigator should use their clinical judgment as well as the guidelines in Table 3 to assess the relationship between Study Drug and Adverse Event.

**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 Adverse Event. 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 adverse event will be categorized as none, concomitant medication, concomitant procedure, or other (specify).

### 13.6.6 Assessment of Outcome

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

## 13.7 Adverse Event Reporting Procedures

### 13.7.1 All Adverse Events

Any clinically significant adverse event that is ongoing at the time of study completion or early termination will be followed by the Investigator until event resolution, the adverse event is

otherwise explained, not considered clinically significant by the Investigator, or the subject is lost to follow-up.

All AEs identified, whether serious or non-serious, will be recorded in the AE eCRF beginning from the time of first study drug infusion and ending at Day 141 (±3) or ET. SAEs considered related to Screening procedures will be recorded in the AE eCRF starting on the date of informed consent. Whenever appropriate, the CTCAE (v. 5.0 or most current version) should be utilized for naming common AEs (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 will 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 SAEs, and forms should be completed with as much information as is available and submitted to the Sponsor within 24 hours. SAEs should 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 upon initial submission they should be contacted via telephone and their assessment documented on the SAE form (with a note stating signature is forthcoming). The Investigator **may change** their causality assessment based on follow-up information and submit an amended SAE reporting 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 subject's condition will be followed by the Investigator or designated Subinvestigator until resolution of the condition or a return to baseline levels. If additional visits are required, the subject will be asked to return to the study site for further follow-up. If the condition is still ongoing at the time the subject exits the study, every effort will be made to continue to follow up with the subject for a reasonable period of time, as determined by the Investigator or until there is a return to baseline or stabilization of the condition. As additional information becomes

available, such as hospital discharge notes and patient medical records, the Investigator will be notified and provided with all relevant information.

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

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value is available.
- The event can be attributed to agents other than the investigational product or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (subject 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**

Phone: +1 443-699-5230

Fax: +1 888-237-7475

E-mail: SAE@allakos.com

### 13.7.3 Pregnancy Reporting

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

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

Any congenital abnormalities noted at birth in the offspring of a subject who received study drug will be reported as an SAE. The outcome of any pregnancy and the presence or absence of any

congenital abnormality will be recorded in the source documentation and reported to the Medical Monitor and Sponsor.

### 13.7.4 AESI Reporting

Beginning from the time of first study drug infusion and ending at Day 141 (±3 days) or the ET Visit or the end of the Extended Follow-Up period if applicable, any new AESI (or new information related to a previously reported AESI) must be recorded in the 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. AESIs that are also SAEs 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. [redacted] should be contacted directly using the phone numbers and/or email address below to report medical concerns or for questions regarding safety.

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

## 13.9 Independent Data Monitoring Committee

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

## 13.10 Study Withdrawal Criteria

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

- Occurrence of an exclusion criterion, which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor.
- Rebounding of eosinophil counts to >1500/μL in subjects who entered the study with eosinophil levels >1500/μL, had an infusion-related reaction during the first and/or second infusion, and whose eosinophil counts were initially suppressed after study drug will be withdrawn from the study at the instruction of the unblinded 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 IRBs will be informed about the discontinuation of the trial in accordance with applicable regulations. The trial may be terminated or suspended on request of Health Authorities or Sponsor.

## 14. Discontinuation and Replacement of Patients

### 14.1 Definition of Study Completion

A subject who completes visits through the Day 141 visit or the end of the Extended Follow-Up period after completing Day 141, if applicable, will be recorded as having completed the study.

A subject who completes the study through the Day 113 Visit and enrolls in the AK002-003X extension protocol will be categorized as having completed the AK002-003 study.

### 14.2 Early Discontinuation of Study Drug

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

- Subject withdraws consent.
- AE that, in the opinion of the Investigator, results in it being in the best interest of the subject to discontinue study treatment.

- Protocol violation requiring discontinuation of study treatment.
- Participation in any other trial during the duration of this trial.
- Use of a non-permitted concomitant drug, without prior approval from the Medical Monitor.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

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

All subjects who discontinue study drug treatment should be encouraged to continue on study and complete assessments and procedures according to the 8-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 subject withdrawals. The reason for the subject's withdrawal from the study, or all attempts to acquire such, will be specified in the source documents.

## 15. Statistical Methods and General Considerations

This section outlines the nature and rationale for the statistical methods to be used for the analysis of the data from the study. A separate Statistical Analysis Plan (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 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% confidence intervals will be provided for the mean and proportion. No formal statistical inferences will be made for safety parameters. No imputation will be used for missing data.

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

### 15.1 Sample Size

Assuming a reduction of 30% in the number of eosinophils per HPF (primary endpoint) from baseline in the AK002-treated group versus a 10% reduction per HPF in the placebo group, and assuming a standard deviation of 20%, 20 subjects per group would provide 87% power with a significance level of 0.05. Hence, 20 subjects per group would be more than adequate from an efficacy perspective.

### 15.2 Data Sets Analyzed

All subjects who have received study medication will be included in the Safety population for safety analysis. Subjects who are randomized and have received at least one dose of study medication and have a post-baseline efficacy assessment will be included in the Modified Intent-to-Treat (MITT) population for efficacy analysis. The study statistician along with the study team will review protocol deviations to identify subjects to be excluded from the per Protocol Analysis population.

### 15.3 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

### 15.4 Subject Disposition

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

### 15.5 Analysis of Safety Endpoints

**Adverse Events:** All AEs 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 AEs collected on study. The summaries of AEs will be based on TEAEs, defined as an AE reported in the clinical database with a date of onset (or worsening) on or after the start date of the first IV infusion of the study medication.

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

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

**Clinical Laboratory Assessments:** Samples will be obtained for the clinical laboratory tests identified in Section 11.4, and laboratory tests to be summarized include 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.

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

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

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

**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.

### 15.6 Efficacy Analysis

**Primary Efficacy Endpoint Analysis:** The primary efficacy analysis is the percent change from baseline in the number of eosinophils per HPF in gastric or duodenal mucosa. For subjects 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 99. For subjects who provide both gastric and duodenal biopsies, the calculation will be based on the average count of the highest readings from the combined pool of gastric and duodenal mucosa. This endpoint will be summarized by treatment group. Between dose and placebo group comparisons in the percent change will be carried out by analysis of covariance (ANCOVA) with baseline value and randomization stratum as covariates. Missing eosinophil counts at Day 99 will be multiply imputed using baseline, randomization stratification, and other relevant variables as covariates.

Sensitivity analyses will be carried out to demonstrate the robustness of the treatment effect:

- The Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification variable.
- A responder analysis by the CMH test, where the responder is defined as the eosinophil count $\leq$30 cells/HPF.
- The ANCOVA of the log-transformed number of eosinophils as the response variable and log-transformed baseline and primary diagnosis as covariates.
- A sensitivity analysis that is similar to the primary analysis. Instead of assuming missing at random, this analysis assumes missing not at random in the multiple imputations.

To control for the type-1 error, the Gatekeeping procedure will be followed. Specifically, the high-dose group (Treatment Group 1, Section 3.2.1) will be compared to the placebo group at the 2-sided $\alpha$=0.05 level first. If this comparison is statistically significant, the low-dose group (Treatment Group 2) will be compared to the placebo group also at the 2-sided $\alpha$=0.05 level. If the first comparison does not demonstrate statistical significance, the second comparison will automatically be considered not significant.

The Gatekeeping procedure is added for multiplicity adjustment due to the comparison of 2 dose groups to the placebo group.

The method of multiple imputations for missing data is added to the primary endpoint and the first secondary endpoint analyses.

**Secondary Efficacy Endpoint Analyses:** The total symptom score (TSS), the composite score of interest (CSI), and the domain scores of the PRO symptom intensities will be summarized

weekly for each patient. The weekly change scores will be analyzed using the MMRM model with treatment, visit, and treatment-by-visit interaction as fixed factors, baseline as covariates, and subject as repeated measure unit.

The comparison between the active dose groups and the placebo group will be based on the averages of the last 6 weeks (Weeks 9 through 14), and the last 2 weeks (Weeks 13 and 14) prior to biopsy, for weekly TSS, CSI, and symptom scores using simple contrasts. P-values and confidence intervals will be presented without multiplicity adjustment. Details of the analytical methods will be included in the SAP.

A responder analysis comparing AK002 and placebo will be performed. A responder is a patient who exhibits a >30% reduction in CSI (abdominal pain, nausea, and diarrhea) and a >75% reduction in mucosal eosinophils.

Baseline for PRO will be calculated using all PRO assessments collected prior to randomization.

Change in the number of [redacted] from baseline will be analyzed using the same MMRM method.

Change in the number of eosinophils in gastric mucosa in patients with EG and in duodenal mucosa in patients with EGE will be analyzed using the same method as for the primary efficacy endpoint.

### 15.7 Subject Confidentiality

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

Only the PID, subject initials, and demographics will be recorded in the eCRF. If the subject name appears on any source document collected (e.g., hospital discharge summary), it must be removed from the document if the document will be viewed by the Sponsor or a sponsor-contracted study vendor not permitted access to subject identifying information. All study findings will be stored in electronic databases. The subjects will give explicit written permission for representatives of the Sponsor, regulatory authorities, and the IRB to inspect their medical records to verify the information collected. Subjects will be informed that all personal information made available for inspection will be kept confidential to the extent permitted by all applicable state, local, and federal data protection/privacy laws and/or regulations and will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

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

## 16. Data Collection, Retention, and Monitoring

### 16.1 Data Collection Instruments

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

### 16.2 Data Management Procedures

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

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

### 16.3 Data Quality Control and Reporting

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

### 16.4 Database Lock/Disclosure of Randomization Code

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

- All records are entered in the database.
- All adverse events are coded to the satisfaction of the Chief Medical Officer.
- All medications are coded to the satisfaction of the Chief Medical Officer.
- All data queries have been resolved.
- All decisions have been made regarding all protocol violations and ITT population exclusions.

- Written authorizations to lock the database are obtained from Allakos Clinical Data Management and the Chief Medical Officer. The randomization code for this study will not be revealed until the previous preconditions are fulfilled and documentation of the database lock is complete.

### 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
- IEC Documents
- Drug Accountability
- Correspondence
- Medical Reports
- Patient Data
- Monitoring Visit Reports
- Sample CRFs 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.

## 17. Administrative, Ethical, and Regulatory Considerations

The study will be conducted in a manner consistent with the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), IRB (21 CFR 56 and ICH E6), and Obligations of Clinical Investigators (21 CFR 312 and ICH E6). The Investigator must also comply with all applicable privacy regulations (e.g., the 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. Any Protocol Amendments must also be signed by the Investigator.

### 17.2 Independent Ethics Committees

The protocol and ICF will be reviewed and approved by the Institutional Review Board (IRB) of each participating study site prior to study initiation. A Central IRB may be used if permitted by the participating study site. All SAEs, 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, ICFs, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRBs written unconditional approval of the study protocol and the ICF will be in the possession of the Investigator before the study is initiated. The IRB's approval of the Investigational site must be available to Allakos prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

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

### 17.3 Informed Consent Form

Prior to study enrollment, all subjects must consent to participate.

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

The process of obtaining the informed consent will be comply with all federal regulations, ICH requirements, and local laws.

The Investigator or a designee will review the study and the ICF with each potential subject. The review will include the nature, scope, procedures, and possible consequences of participation in the study. The consent and review must be in a form understandable to the potential subject. The Investigator or designee and the subject must both sign and date the ICF after review and before the subject can participate in the study. The subject will receive a copy of the signed and dated form, and the original will be retained in the site's study files. The Investigator or designee must emphasize to the subject that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

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

### 17.4 Publications

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

### 17.5 Clinical Trial Registration

This clinical trial is registered on the Clinical Trial Registry Website, www.ClinicalTrials.gov, NCT #03496571.

### 17.6 Payment to Subjects

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

### 17.7 Investigator Responsibilities

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

1) Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights, or welfare of 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 AEs that occur in the course of the study, in accordance with 21 CFR Part 312.64 and ICH Guideline E2A.

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

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

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

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

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

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

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## 19. Appendices

## 19.1 Appendix 1: PRO Questionnaire

**EOSINOPHILIC GASTRITIS AND GASTROENTERITIS DISEASE PATIENT-REPORTED OUTCOME QUESTIONNAIRE**

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

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

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

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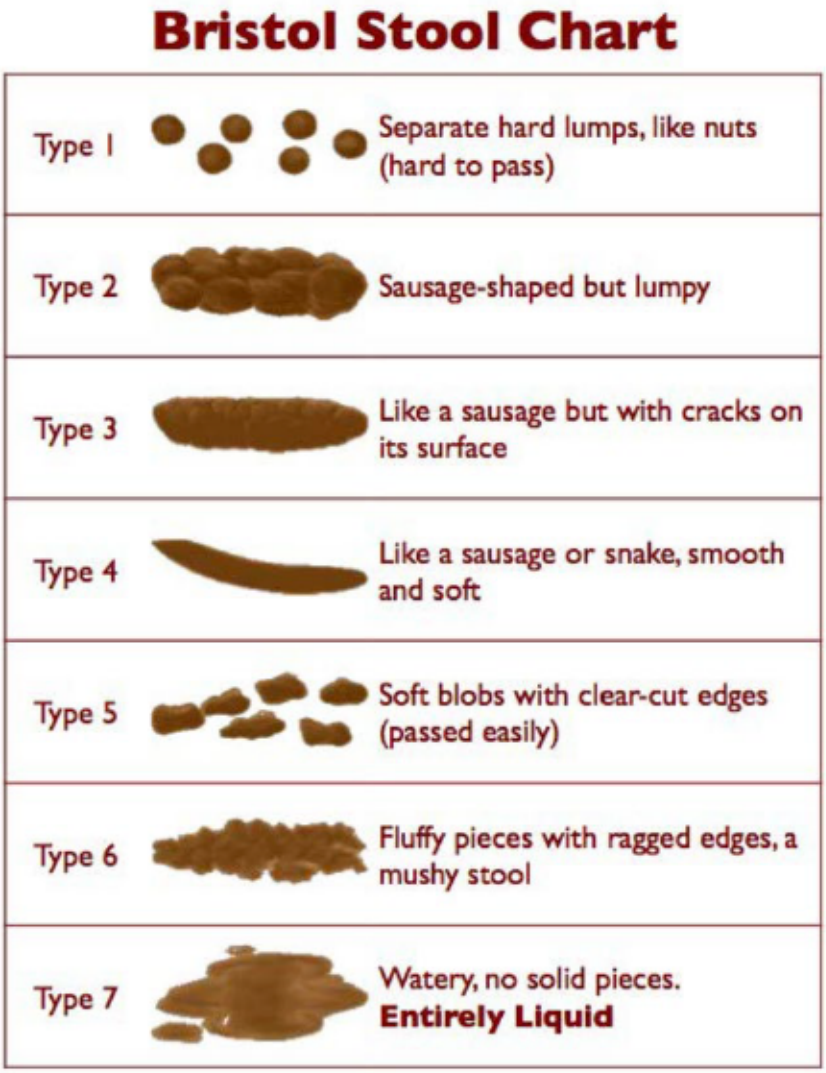
## Appendix 1: PRO Questionnaire cont.

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

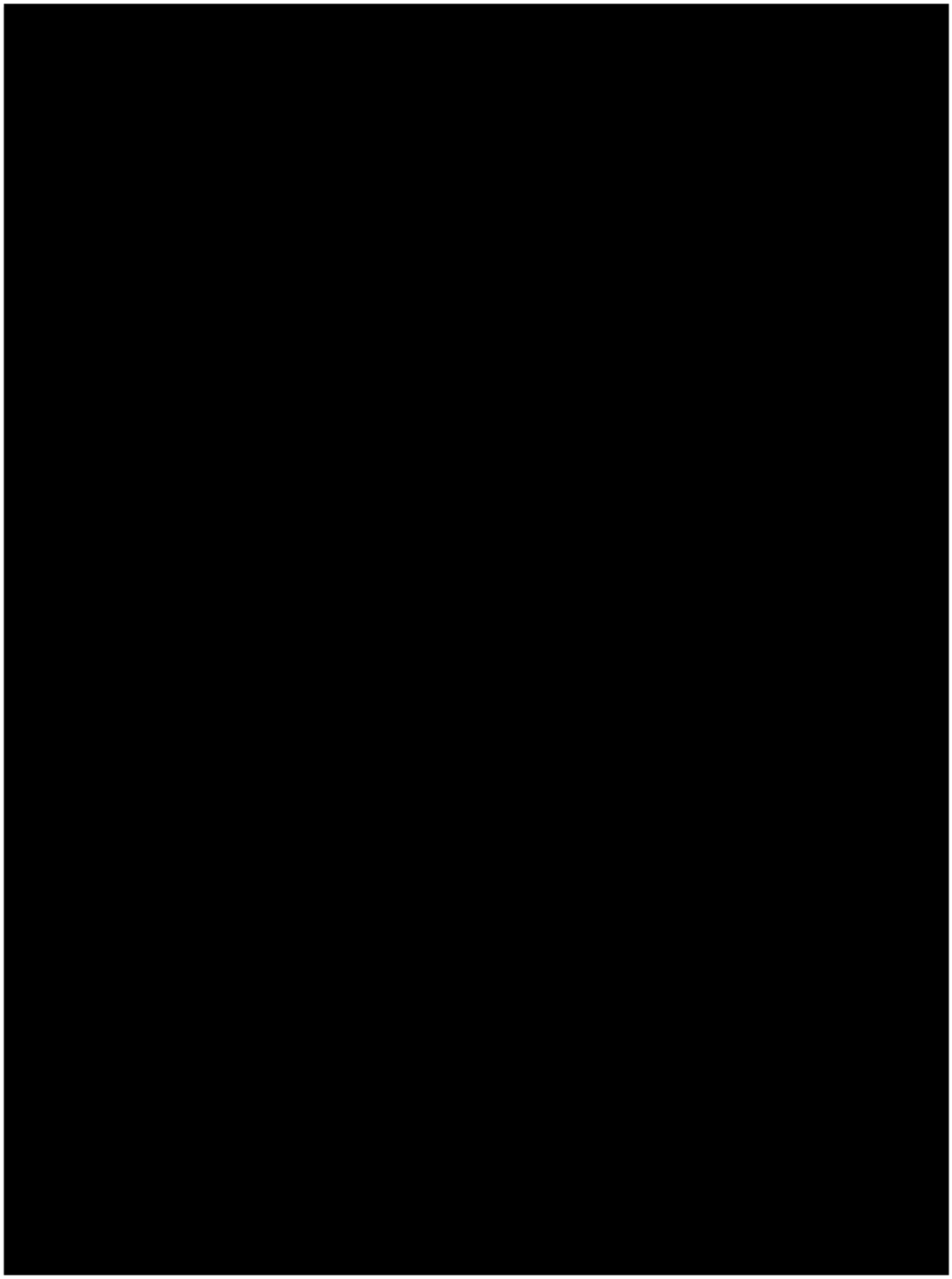
**Appendix 1: PRO Questionnaire cont.**



## 19.2 Appendix 2: [redacted]

[redacted]

**Appendix 2: [redacted] cont.**



**Appendix 2: [redacted] cont.**

[redacted]

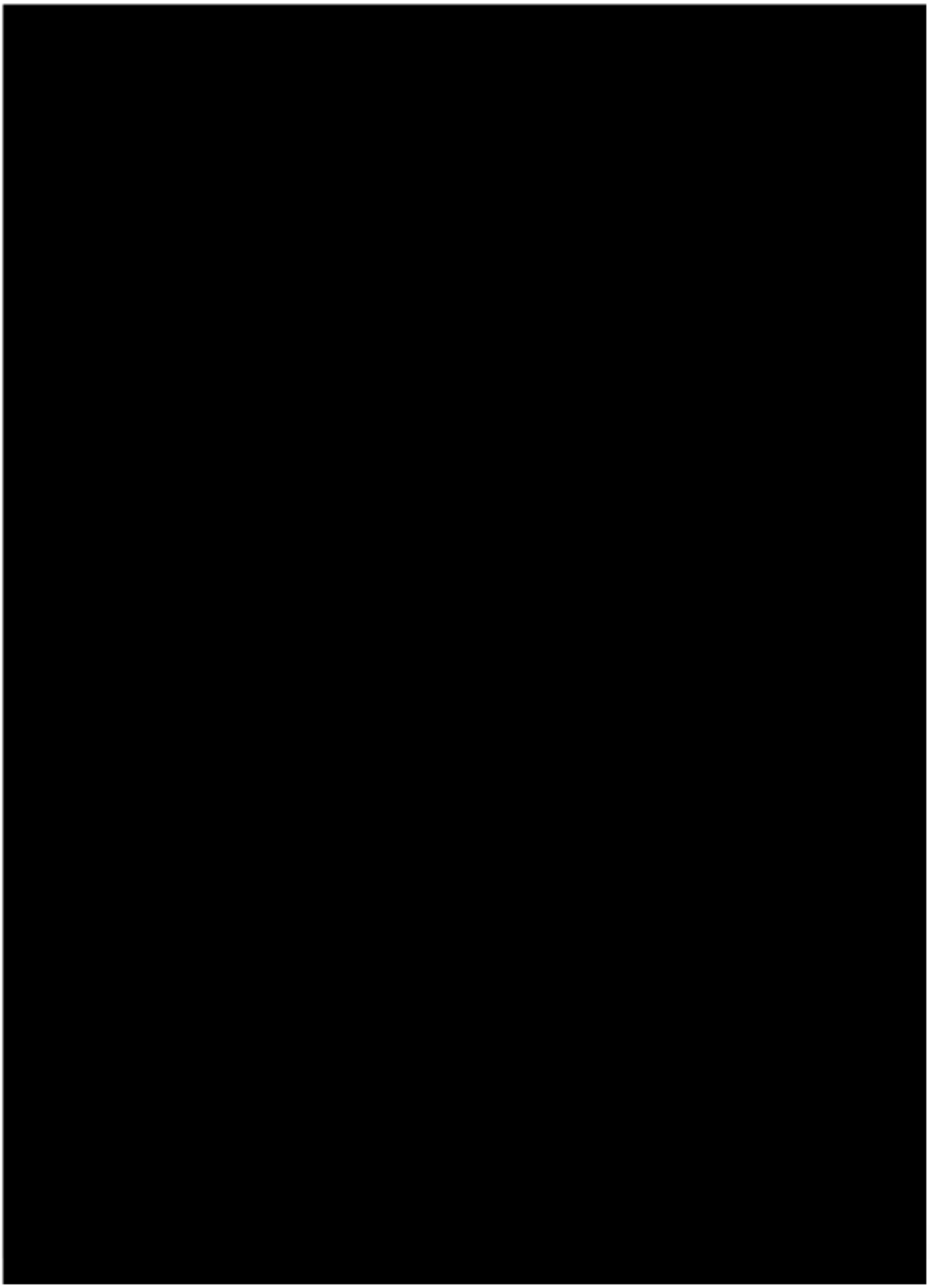
**Appendix 2: [redacted] cont.**

[redacted]

**Appendix 2: [redacted] cont.**

[redacted]

**Appendix 2: [redacted] cont.**



## 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 the Screening Period.

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

   If Yes, what is the diet?

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

   ☐ 6-food or 3 Food Elimination Diet

   ☐ Supplemental Protein Shake/drink specify: _____

   ☐ Other; describe: _____

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

   If Yes, what are they? _____

   _____

3. **Does eating certain foods seem to make your EG/EGE <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/EGE?** 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/EGE?** 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.

**Staining**

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

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

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

- **Esophagus** (ONLY if subject has concomitant EoE)
  - A set of 2 fragments from the distal esophagus
  - A set of 2 fragments from the mid-proximal esophagus.
  - Up to 2 extra specimens may be collected if there are any additional areas of interest

  A count of ≥15 eosinophils per HPF in at least one esophageal site will be considered diagnostic of eosinophilic esophagitis.
- **Stomach**
  - A set of 4 specimens from separate areas of the gastric antrum (2–5 cm proximal to the pylorus)
  - A set of 4 specimens from separate areas of the gastric corpus (two from the proximal lesser curvature and two from the greater curvature)
  - Up to 2 extra specimens may be collected if there are any additional areas of interest

  A count of ≥30 eosinophils per HPF in at least 5 HPFs will be considered diagnostic of eosinophilic gastritis.
- **Duodenum**
  - 4 fragments of duodenal mucosa from the second and third part of the duodenum.
  - Up to 2 extra specimens may be collected if there are any additional areas of interest

  A count of ≥30 eosinophils per HPF in at least 3 HPFs will be considered diagnostic of eosinophilic gastroenteritis.

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

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

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

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

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

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

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

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

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

**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):

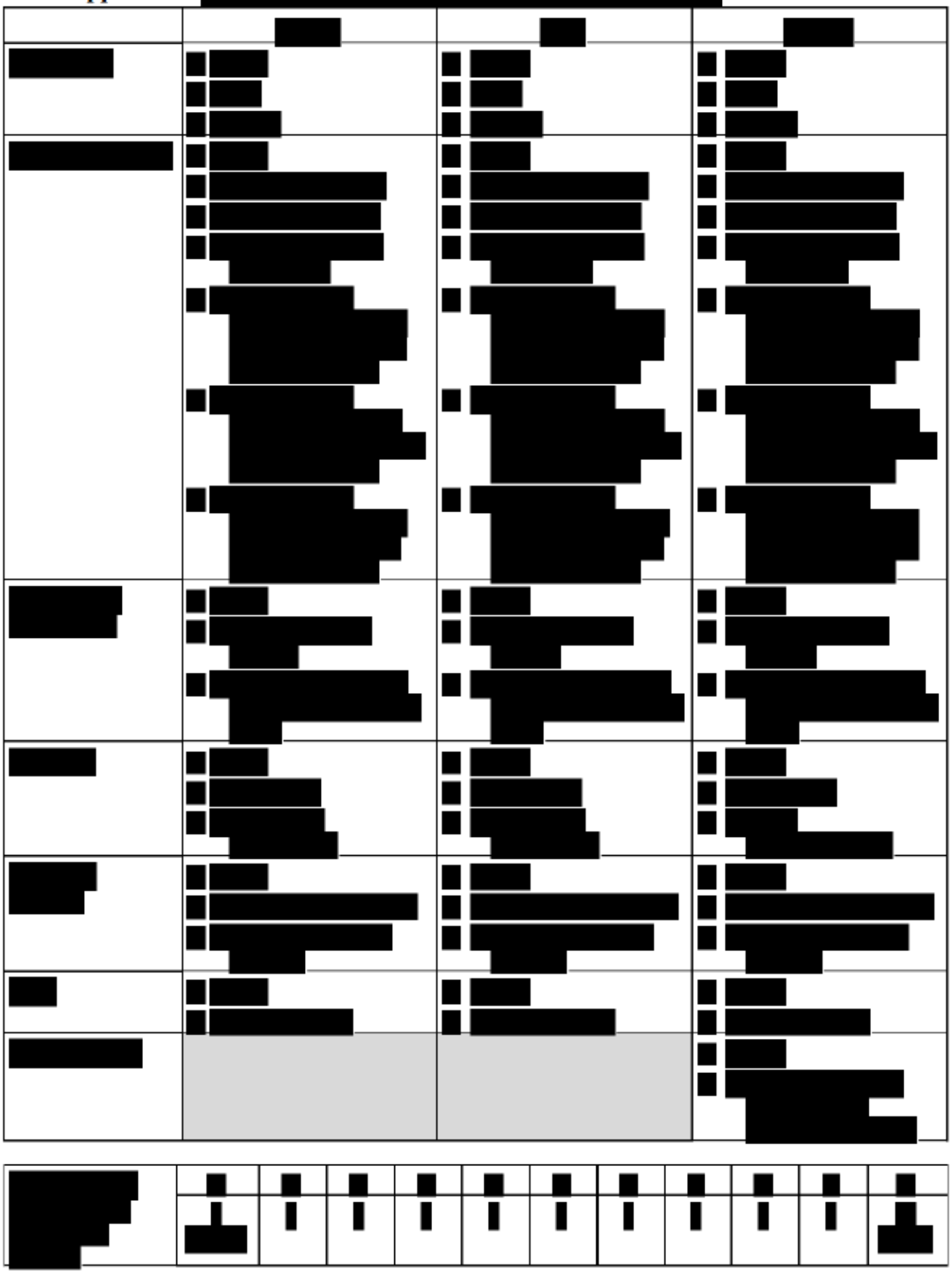
- **RESPIRATORY**: Airway compromise (e.g., dyspnea, wheeze, or bronchospasm, stridor, reduced PEF, hypoxemia)
- **CIRCULATORY**: Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope)

**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: [redacted]



## 19.8 Appendix 8: Biomarker Sub-Study for Selected Sites

See Laboratory Manual Sub-Study Memo for complete instructions for collection, processing, and shipping of sub-study laboratory samples.

The following samples may be collected for the sub-study:

**Blood Samples**

Plasma from whole blood

- Collect 10 mL of blood at Baseline and Day 99 (prior to Endoscopy).
- Send frozen to ICON Central Laboratory.

Serum from whole blood

- Collect 10 mL of blood at Baseline and Day 99 (prior to Endoscopy).
- Send frozen to ICON Central Laboratory.

**Urine Samples**

- Collect at Baseline, Day 99 (prior to endoscopy) and pre and post-dose on Infusion Days 1, 29, 57, and 85.
- Send frozen to ICON Central Laboratory.

**Biopsy Samples**

- Collect 2 biopsies from an abnormal-appearing area in the gastric mucosa.
- Send frozen to ICON Central Laboratory.

## 19.9 Appendix 9: Additional Questions for Atopic Conditions

**PROTOCOL AK00-003**
ADDITIONAL QUESTIONS FOR SUBJECTS WITH ATOPIC CONDITIONS

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

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

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