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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Statistical Analysis Plan

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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List of Abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
ADA	Anti-drug antibody
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body mass index
BP	Bodily Pain
CBC	Complete blood count
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRO	Contract Research Organization
CSI	Composite Score of Interest
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
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]
EoE	Eosinophilic esophagitis
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GH	General Health
HPF	High power field
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IV	Intravenous
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intention-to-Treat (population)
MH	Mental Health
MMRM	Mixed Model for Repeated Measures

PCS	Physical Component Summary
PD	Pharmacodynamics
PID	Patient Identification (number)
PE	Physical examination
PF	Physical Functioning
PK	Pharmacokinetic(s)
PT	Preferred term
PRO	Patient-reported outcome
p-value	Probability value
QoL	Quality of Life
RE	Role-Emotional
RP	Role-Physical
SAE	Serious adverse event
SD	Standard deviation
SAP	Statistical Analysis Plan
SF	Social Functioning
[redacted]	[redacted]
SOC	System organ class
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse event of significant interest
TESAE	Treatment-emergent serious adverse event
TLF	Tables, Listings, and Figures
TSS	Total Symptom Score
VT	Vitality
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

Revision History

Version Date	Version Number	Description
28 Aug 2018	1	First version of the Statistical Analysis Plan
29 May 2019	2	1. Updated to match with the protocol amendment 6 2. Clarified how the "14 days following last dose/2 weeks prior to biopsy" for PRO CFB analysis is defined 3. Removed ITT population 4. Added Treatment Responder as the 1st secondary endpoint and classified TSS as the 2nd secondary endpoint 5. Removed previous 7.10.3 Sensitivity Analysis 2 with missing data imputed based on MNAR assumption and Sensitivity Analysis 3 using log-transformed data for the primary endpoint 6. Removed previous 7.10.4 Subgroup Analysis for the primary endpoint 7. Replaced "change from baseline" with "percent change from baseline" for the secondary endpoints 8. Clarified 7.11.1 for how % change in TSS at end of treatment is calculated. Replaced MMRM with ANCOVA. Removed sensitivity analysis with missing data imputation 9. Added subgroup analysis for the 1st secondary endpoint 10. Expanded Exploratory Endpoints to include [redacted] for the [redacted], and [redacted] 11. Revised the language for the ADA analysis.

1. Introduction

This statistical analysis plan (SAP) describes the rules and conventions to be used in the analysis and presentation of efficacy, safety, tolerability, and pharmacodynamic data as planned for the clinical protocol. It describes the data and variables to be summarized or analyzed, including specifications of the analytical methods to be performed. The SAP presented in this document supersedes the statistical analysis methods described in the clinical protocol. Significant deviations/changes from the planned analyses described in this SAP will be identified, with justification, in the appropriate section of the clinical study report (CSR). This SAP is based on the clinical study protocol AK002-003 Amendment 6, dated 07 February 2019, and its associated electronic case report forms (eCRF).

2. Study Objectives

2.1 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 biopsies before and after receiving AK002 or placebo.
2) The safety and tolerability of AK002 in patients with EG and/or EGE.

2.2 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) Compare treatment responders between AK002 and placebo; a responder is a patient who exhibit a >30% reduction in Total Symptom Score (TSS) (all PRO symptoms) and a >75% reduction in mucosal eosinophils.
2) Changes in EG/EGE symptoms in a Patient Reported Outcome (PRO) questionnaire.

2.3 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) Change in [redacted].
2) Changes in [redacted] in a Patient Reported Outcome (PRO) questionnaire.
3) Number of [redacted] in patients with [redacted].
4) [redacted] before and after treatment.
5) Change in [redacted], respectively.

6) Change in [redacted].
7) Change in [redacted] and [redacted]
8) Scoring of [redacted] using the [redacted]

2.4 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.

3. Study Design

3.1 General Description

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled study. The study comprises a screening period of 21 to 35 days with baseline evaluations for study eligibility. If subjects meet histology and symptom eligibility criteria, they will receive 4 doses of AK002 or placebo by IV infusion on Days 1, 29, 57, and 85. Subjects will be followed for 56 days after last dose. Follow-up visits will occur on Days 113 and 141.

If the absolute lymphocyte 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 for a follow-up safety visit.

Total study duration will be up to approximately 23–25 weeks.

The study design is presented schematically 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][11]	X	X (pre-dose)			X (pre-dose)	X (pre-dose)	X (pre-dose)		X	X	
EGD with Biopsy[12, 13]	X							X			
[redacted][14]	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 Protocol 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.

3.2 Study Treatment

3.2.1 Treatment, Dose, and Mode of Administration

- Treatment Group 1: 0.3 mg/kg AK002 on Day 1 followed by 1 mg/kg on Day 29, followed by 3 mg/kg on Days 57, and 85
- Treatment Group 2: 0.3 mg/kg AK002 on Day 1 followed by 1 mg/kg on Days 29, 57, and 85
- Treatment Group 3: Placebo on Days 1, 29, 57, and 85

3.2.2 Duration of Study

Total subject duration on study is approximately 23–25 weeks.

- Screening phase: 21–35 days
- Treatment phase: 85 days (±3 days)
- Follow-up after last dose: 56 for subjects who do not enroll in the AK002-003X extension study or 28 days (±3 days) for subjects who enroll in the AK002-003X extension study. If the absolute lymphocyte 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.

3.2.3 Methods of Assigning Subjects to Treatment Group

Approximately 60 subjects will be stratified based on the highest weekly average of the qualifying symptom of disease recorded on the PRO questionnaire during the screening period (PRO score 3–4.9, or 5.0–10.0) and randomized in a 1:1:1 ratio to Treatment Groups 1, 2, and 3 (Section 3.2.1).

3.3 Blinding

This is a double-blind study. The identity of test and placebo treatments will not be known to investigators, sponsor, research staff, subjects, or the primary study monitor. Only the unblinded study pharmacist, the unblinded pharmacy monitor and the unblinded safety monitor will know the treatment assignment.

3.4 Hypotheses

The hypothesis to be tested in the study is that AK002, in either one or both of the 2 doses, are different from placebo with regard to the primary endpoint of number of eosinophils per HPF in biopsies from the gastric mucosa.

3.5 Determination of Sample Size

Assuming a reduction of 30% in the number of eosinophils per HPF (primary endpoint) from baseline in the AK002-treated group (Treatment Group 1 or 2) versus a 10% reduction per HPF in the placebo group (Treatment Group 3), and assuming a standard deviation of 20%, 20 subjects per group would provide 87% power with a significance level of 0.05.

3.6 Changes to Analyses Planned in the Protocol

The protocol-defined gatekeeping procedure of high dose then low dose comparison to placebo for the primary endpoint is revised to include high/low pooled, high, and low dose comparisons to placebo for the primary and secondary endpoints.

The protocol-defined treatment responder is now classified as the 1st secondary endpoint and percent change from baseline to end of treatment in TSS is now the second (2nd) secondary endpoint. Other protocol-defined secondary endpoints are now moved to the exploratory endpoints.

The protocol-defined MITT population is now replaced with Per Protocol population for efficacy analysis.

4. Definitions

Table 2 Terminology and Definitions

Terminology	Definition
Study Medication/Drug (SM)	AK002 or placebo administered by IV infusion.
Study Day	Study Day 1 is defined as the date on which a subject took the first dose of SM. Other study days are defined relative to Study Day 1. For visits prior to the first dose of the SM, Study Day is calculated as Visit Date – Day 1 Date. For visits after the first dose, Study Day is calculated as Visit Date – Day 1 Date +1.
Enrolled	Subject who is randomized to a treatment group.
Completer for the Study	Subject who completes visits through the Day 113 Visit and enrolls in the AK002-003X extension study OR a subject who does not enter the AK002-003X extension study but completes the Day 141 visit.

Terminology	Definition
Baseline	Baseline for non-daily assessment (eg, laboratory tests and [redacted]) is defined as the non-missing value collected most recent to and before the time of the very first dose of the study drug. Baseline for daily assessment (eg, ePRO) is defined as the average of all assessments prior to the first dose of the study drug. Baseline for biopsy results is found in the respective analysis section.
Prior Medication	Medication collected on the Prior/Concomitant Medication CRF, with start date prior to Study Day 1.
Concomitant Medication	Medication collected on the Prior/Concomitant Medication CRF, with end date on/after Study Day 1. Note a Prior Medication may also be a Concomitant Medication if the start date is prior to Study Day 1 and end date is on/after Study Day 1.
Treatment-emergent	Adverse events 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 SM.
Patient Reported Outcome (PRO)	PRO questionnaire evaluates 8 different symptoms with 10 daily questions for intensity and frequency: • 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 Each intensity evaluation is scored on a scale of 0=none to 10=worst possible.
PRO Total Symptom Score (TSS)	TSS is the sum of 8 (abdominal pain, abdominal cramping, bloating, nausea, vomiting, diarrhea, early satiety, and loss of appetite) weekly average symptom intensity scores.

Terminology	Definition
PRO Composite Score of Interest (CSI)	CSI is the sum of the 3 (abdominal pain, nausea, and diarrhea) weekly average symptom intensity scores of special interest.
Treatment Responder	Subject with >30% reduction in TSS score combined with a >75% reduction in eosinophils in the gastric and/or duodenal mucosa. The eosinophil count is obtained on Day 99 (Week 14) biopsy and the TSS score for the analysis will be the average of the 14 daily scores starting with the day of the last dose to the day before the end of study biopsy. If a minimum of 7 daily scores are not recorded in this nominal 14-day window, the window will be rolled back until a minimum of 7 scores are present. For patients whose biopsy is collected prior to Day 99 due to early discontinuation, the average of the last 14 days of TSS scores recorded for that patient will be used for the analysis.
Study Week	Study Week for PRO analysis is defined as 7 days a week starting from the day of first dose (Day 1).

5. Study Endpoints

5.1 Primary Efficacy Endpoint

Percent change from baseline in the number of eosinophils per HPF in gastric mucosa or duodenal mucosa at Week 14 (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 Day 99/End of study biopsy that correspond in location (gastric or duodenal) to the location with the highest average count at baseline.

5.2 Secondary Efficacy Endpoint

1st Secondary Endpoint

Proportion of Treatment Responders, defined as patients with >30% reduction in TSS score combined with a >75% reduction in eosinophils in the gastric and/or duodenal mucosa. The eosinophil count is obtained on Day 99 (Week 14) biopsy and the TSS score for the analysis will be the average of the 14 daily scores starting with the day of the last dose to the day before the end of study biopsy. If a minimum of 7 daily scores are not recorded in this nominal 14-day window, the window will be rolled back until a

minimum of 7 scores are present. For patients whose biopsy is collected prior to Day 99 due to early discontinuation, the average of the last 14 days of TSS scores recorded for that patient will be used for the analysis.

2nd Secondary Endpoint

Percent change from baseline in the TSS scores averaged over the 14 daily scores starting with the day of the last dose to the day before the end of study biopsy. For patients whose biopsy is collected prior to Day 99 due to early discontinuation, the average of the last 14 days of TSS scores recorded for that patient will be used for the analysis. (See 1st Secondary Endpoint for the calculation of TSS average.)

5.3 Exploratory Endpoints

- Change from baseline in the [redacted] counts by visit.
- Change from baseline in the [redacted] scores averaged over the 14 daily scores starting with the day of the last dose to the day before the end of study biopsy. For patients whose biopsy is collected prior to Day 99 due to early discontinuation, the average of the last 14 days of scores recorded for that patient will be used for the analysis. (See 1st Secondary Endpoint for the calculation of average.)
- Percent change from baseline in the [redacted] scores averaged over the 14 daily scores starting with the day of the last dose to the day before the end of study biopsy. For patients whose biopsy is collected prior to Day 99 due to early discontinuation, the average of the last 14 days of [redacted] scores recorded for that patient will be used for the analysis. (See 1st Secondary Endpoint for the calculation of [redacted] average.)
- Percent Change from baseline to Week 14 (Day 99) in the number of [redacted] in patients with [redacted].
- Proportion of
  - EG patients with average [redacted] per HPF in [redacted],
  - EGE patients with average [redacted] per HPF in [redacted], and
  - EoE patients with average [redacted] per HPF in [redacted].
- [redacted] before and after treatment.
- Change from baseline to Week 14 (Day 99) in the number of [redacted] in
  - [redacted],
  - [redacted]

- [redacted].
- Change from baseline in the scoring of [redacted] using the [redacted].
- Changes from baseline to Week 14 (Day 99) in [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted].
- Change from baseline in the [redacted] for patients with [redacted]
- Percent changes from baseline in the [redacted] and [redacted] for averages of Weeks 13-14, 11-14 and Weeks 9-14 and separately for each individual week.
- Changes from baseline in the [redacted] for averages of Weeks 13-14, 11-14 and Weeks 9-14 and separately for each individual week.
- Change from baseline in [redacted] over time.
- [redacted] at baseline and Day 99.
- Distribution of [redacted] in the histological findings at Day 99.

5.4 Pharmacokinetic (PK) Endpoints

- Serum concentrations of AK002 prior to each dose and on Days 15, 113 and 141 (or ET).

5.5 Safety Endpoints

Safety endpoints include:

- Treatment-emergent adverse events (TEAEs)
- Change in laboratory test results (Hematology, Blood chemistry, Urinalysis)
- Changes in vital signs

- Physical examination
- Anti-drug (AK002) antibody (ADA)
- Concomitant medication

6. Statistical Methods

6.1 General Methodology

All statistical analyses will be conducted using SAS v 9.4 or later version on the Microsoft Windows Operating System.

All CRF data (raw data) will be converted into SDTM (Study Data Tabulation Model) datasets, which will be used to create ADaM (Analysis Data Model) data sets. The creation of the SDTM and ADaM data sets will follow the CDISC (Clinical Data Interchange Standards Consortium) standards and the FDA Study Data Techinical Conformance Guide. All analysis tables and listings will be created from the ADaM data sets.

Continuous data will be summarized using n (number of subjects with non-missing observations), mean, median, standard deviation (SD), minimum value, and maximum value. Categorical data will be summarized using the frequency count and percentage (n, %) of subjects in each category. Number of subjects with non-missing values or number of subjects with missing values (e.g., Not Done) will be presented, where appropriate. Subjects with missing values will not contribute to the denominator for percentage calculations, unless specified otherwise. Counts of zero in any category will be presented without percentage. All summaries will be presented for individual treatment groups. In addition, for summary of disposition and subject baseline characteristics, the presentation will include all 3 groups combined. For summary of efficacy and safety endpoints, the presentation will include both active dose groups combined.

The precision rules for the presentation of summary statistics will be:

- Sample size (n, N) and number of missing responses (if displayed) – Integer
- Mean, confidence interval, and median – One more decimal place than reported/collected
- Standard deviation – Two more decimal places than reported/collected
- Percentiles, minimum, maximum – Same number of decimal places as reported/collected
- Ratio – two decimal places
- Percentage – one decimal place generally, or two decimal places for <0.1%

The data summaries will be accompanied by individual subject data listings. All data available from questionnaires, eCRF, and external transfer (labs) will be listed and will include relevant subject information, e.g., treatment group and study day. The listings will be sorted in the order of subject ID, and assessment date/time and assessment name.

For each summary table, a supporting listing will be identified in the footnote.

Dates will be presented in the ISO-8601 format YYYY-MM-DD. Times will be displayed in 24-hour clock format. Numbering for tables, figures and listings will follow ICH E3 Guideline (ICH, 1996).

Alternative methods of analysis of the data may be considered prior to database lock should some of the assumptions underlying the proposed analyses not be met. Reason for departure from the planned methods will be documented as an amendment to the SAP or in the CSR.

6.2 Visit Window and Unscheduled Assessments

There is no visit window for the by-visit analysis. Data will be analyzed according to the visit they are associated with, unless specified otherwise.

6.3 Adjustment for Covariates

Baseline and randomization stratum may be adjusted, where appropriate, in estimating the between group difference using ANCOVA, MMRM, or Cochran-Mantel-Haenszel tests.

6.4 Handling of Dropouts, Missing Data, and Data Discrepancies

For the exploratory endpoints of percent change in the weekly [redacted], when ≥3 of 7 daily scores are available, the weekly average score will be calculated using the available daily scores. This calculation implies the missing daily scores are the same as the mean of the non-missing daily scores. When >4 daily scores are missing, the weekly score will be set to missing. For the weekly [redacted], when ≥4 of 8 weekly [redacted] scores are available, [redacted] will be calculated using the available weekly [redacted] scores. Otherwise, the weekly [redacted] will be set to missing. For the [redacted], Section 6.9), when ≥2 weekly [redacted] scores are available, [redacted] will be calculated using the available weekly [redacted] scores. Otherwise, [redacted] will be set to missing.

The exploratory analysis for the [redacted] will be based on the [redacted] model (Section 6.9). Except for the implicit imputation described above, no imputation will be applied to the missing data. Under the MAR assumption, the [redacted] analysis is considered unbiased.

AEs with incomplete start or stop dates (i.e., either day or month is missing) will be considered treatment-emergent (TEAE) unless the partial start date or the stop date confirms the AE started or ended prior to Study Day 1 (e.g., the day of the AE start date is unknown but the month and year indicate that the AE starts prior to Study Day 1). AEs with missing relationship to study drug will be included in the "Related" category for the summary tables. AEs with missing severity will not be included in the by-severity summary table but will be footnoted in the table.

When there is incomplete information regarding dosing dates for prior and concomitant medication, the medication will be considered as a concomitant medication unless it contradicts with the stop date. For example, a medication will be considered a prior medication if the month and year of the end date indicates a date before Study Day 1 even though the start date could be missing.

6.5 Interim Analysis

No interim analysis is planned.

6.6 Timing of Final Analyses

Data analysis will commence after all subjects have completed the study and the study database is cleaned and locked for the data prior to the extended follow-up. Note the PK and ADA data may be locked separately.

6.7 Multicenter Study

This is a multicenter study. Because of small sample sizes for most of the sites, no by site analysis will be performed. All sites will be pooled for data analysis and summary.

6.8 Multiple Comparisons/Multiplicity Adjustment

To control for the family-wise type-I error rate, the following testing procedures will be implemented:

1. Test the high/low dose (Treatment Groups 1 and 2) combined group against placebo (Treatment Group 3) for the primary efficacy endpoint. If $p \leq 0.05$ then proceed to
2. Test the high/low dose combined group against placebo for the 1st secondary efficacy endpoint. If If $p \leq 0.05$ then proceed to
3. Test the high/low dose combined group against placebo for the 2nd secondary efficacy endpoint. If If $p \leq 0.05$ then proceed to
4. Test the high dose against placebo for the primary efficacy endpoint. If $p \leq 0.05$ then proceed to

5. Test the low dose against placebo for the primary efficacy endpoint. If $p \leq 0.05$ then proceed to

6. Repeat above Steps 4-5 for testing the 1st secondary efficacy endpoint, then the 2nd secondary efficacy endpoint.

In the above sequential testing, if any step has $p > 0.05$ then the tests of this step and of all subsequential steps will be considered not statistically significant.

6.9 Examination of Subgroups

Key endpoints may be summarized by subgroup to explore the heterogeneity of the treatment effect across subgroups. Subgroups to be considered are:

- Randomization stratum (baseline highest weekly PRO average score 3–4.9, 5.0–10.0)
- Subjects with EG or EGE alone, EG + EGE, subjects with EoE
- Gender (Male, Female)
- Age (<45, 45 to <65, 65+)
- Baseline peripheral eosinophil counts (<median vs ≥median)

7. Statistical Analysis

7.1 Analysis Populations

The population of "all enrolled subjects" comprises all those who signed informed consent, met all eligibility criteria at Screening, and are randomized to one of the treatment groups.

7.1.1 Safety Population

The safety population comprises all subjects who have signed informed consent and received at least one dose of study drug. All safety endpoints will be analyzed using this population.

7.1.2 Per Protocol Analysis (PP) population

The per protocol population will include all randomized subjects who do not have major protocol deviations adversely affecting the data interpretation. Some examples of PP exclusion criteria are

- Did not receive at least 2 doses of study medication
- Changed dose of systemic steroids and/or started systemic steroid treatment during the study or injections of steroids in the stomach and/or duodenum (this does not include steroids used as premedication the day before and/or the day of study drug infusions).
- Received other prohibited medications (eg, IL-5 inhibitors, dupilumab) potentially impacting efficacy during study treatment

- Did not have at least 6 PROs over 14 day period at any timepoint after administration of second dose.

The study statistician along with the study team will review protocol deviations to identify subjects to be excluded from the per protocol analysis population. The PP exclusion criteria will be updated prior to the database lock and unblinding. The PP population will be specified prior to unblinding using said exclusion criteria.

7.2 Disposition of Subjects

Subject demographics and reasons for screening failure will be summarized for screen-failed subjects.

Subjects (n and %) who completed or discontinued from the study will be tabulated by treatment group and for all 3 groups combined. The primary reasons for study discontinuation will be included in the tabulation. The primary reasons may include, but not limited to, any of the following:

- Subject withdrew consent
- Lost to follow-up
- Administrative reason
- Adverse event
- Investigator decision
- Failure to follow required study procedures
- Other

Subject disposition will be summarized for all enrolled subjects. Subject counts for the Safety and PP populations will be included in the table. A data listing for subject disposition will be presented for all enrolled subjects.

7.3 Protocol Deviations

Protocol deviations will include, but are not limited to

- Non-compliance with any scheduled study visit
- Non-compliance with study treatment
- Received prohibited medications (see Protocol Section 8.1)
- Non-compliance with study inclusion or exclusion criteria
- Non-compliance with study assessment procedures

Subjects with major protocol deviations will be listed. The listing will include a brief description of the deviation, deviation category, and if applicable, study day when deviation occurred along with other pertinent information.

If warranted by the sample size, subjects (n and %) with major protocol deviations will be tabulated by treatment group and by deviation category.

Subjects (n and %) will be tabulated by treatment group for each analysis population. Subjects who are excluded from the PP population will be listed with reasons for exclusion.

7.4 Demographics and Baseline Subject Characteristics

Descriptive statistics for subject characteristics and baseline values will be presented for all populations by treatment group and for all 3 groups combined. Continuous variables will be summarized with n, mean, SD, and median. Categorical variables will be summarized with n and % of subjects for each category, for the Safety and PP populations.

7.5 Baseline Disease Characteristics

Baseline disease characteristics will be included in the subject data listing.

7.6 Medical History

Subject incidence (n and %) of medical history (and current medical condition before signing the informed consent) will be tabulated by MedDRA System Organ Class (SOC) and Preferred Term (PT).

7.7 ECG

A listing of ECG overall interpretation at screening visit will be provided.

7.8 Pregnancy Test

A listing of pregnancy test results will be provided.

7.9 Treatments

7.9.1 Treatment Compliance and Extent of Exposure

Summaries of treatment compliance and exposure to AK002 will be based on the safety population.

Duration of treatment exposure is defined as the total number of days a subject is exposed to the study treatment. This will be calculated for each subject by taking the difference between the date of the last dose minus the date of the first dose, plus 1 (date of last dose – date of first dose +1).

Duration of exposure will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).

Treatment compliance is defined as the number of infusions subjects received divided by 4 (i.e., total number of infusions expected) × 100%. Treatment compliance will be summarized descriptively. In addition, an overall compliance that includes adherence to treatment administration schedule and any interruptions will be included in the data listing.

The treatment infusion information (length, volume, rate, and interruption) will be included in the subject data listing.

7.9.2 Prior and Concomitant Medications

Prior medications and concomitant medications will be extracted from the Prior/Concomitant Medication CRF. Medications taken prior to Study Day 1 will be considered as prior medications and medications taken on or after Study Day 1 will be considered as concomitant medications. Prior and concomitant medications will be coded using WHO Drug Dictionary (WHODD March 2018 release) for Preferred Term (PT) and Anatomical Therapeutic Chemistry (ATC) classification.

Prior and concomitant medications will be tabulated separately based on the Safety Population. The number (n and %) of subjects taking at least one medication and the number (%) of subjects taking each medication at the preferred term level will be tabulated by ATC4, and PT. Subjects taking the same PT medication twice will only be counted once.

A subject data listing will be provided to include the reported medication name, the WHODD PT, ATC4, study day and pertinent subject information.

A separate data listing will include subjects who have received prohibited medications.

7.10 Analysis of Primary Efficacy Endpoint

7.10.1 Primary Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change from baseline to Day 99 in the number of eosinophils per HPF in gastric or duodenal mucosa with biopsy. 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 Day 99 biopsy that correspond in location (gastric or duodenal) to the location with the highest average count at baseline. This endpoint will be summarized by treatment group.

The pooled high/low dose group and each active dose group will be compared to the placebo group in pairwise comparison using analysis of covariance (ANCOVA) model with percent change from baseline as outcome, treatment as factor, and baseline value and randomization stratum as covariates. To control for the type-I error, the Gatekeeping procedure defined in Section 6.8 will be followed.

7.10.2 Secondary Analysis of Primary Efficacy Endpoint

In this analysis, percent change from baseline will be analyzed by the Cochran-Mantel-Haenszel χ^2 (chi-square) test for the row mean score difference stratified by the randomization stratification variable. A sample SAS code for the pairwise comparison is as follows.

```
PROC FREQ ;
        WHERE TRTP IN ('GRP1','PBO') ;
        TABLES RANDSTRA*TRTP*PCHG / CMH SCORE=MODRIDIT RISKDIFF(CL=NEWCOMBE) ;
        ODS OUTPUT CMH=CMHPVAL(WHERE=(ALTHYPOTHESIS='Row Mean Scores Differ')) ;
RUN ;
```

7.10.3 Sensitivity Analyses of Primary Efficacy Endpoint

Sensitivity Analysis

In this analysis, a responder is defined as an eosinophil count <30 cells/HPF. Subjects with missing eosinophil count will be considered non-responders. A logistic regression model with effects of treatment group, randomization stratum, and baseline eosinophil count will be used to analyze the between group difference. Odds ratio and the associated 95% confidence intervals are computed for the comparison of odds of achieving response in the active treatment group against the odds in the placebo group. A sample SAS code:

```
PROC LOGISTIC ;
 CLASS group stratum / PARAM=glm ;
 MODEL resp(REF='0')=group stratum base ;
 ESTIMATE 'Grp 1 - Grp 3' group 1 0 -1 ;
 ESTIMATE 'Grp 2 - Grp 3' group 0 1 -1 ;
 ESTIMATE 'Avg Grp1,2 - Grp 3' group 0.5 0.5 -1 ;
 ODS OUTPUT ESTIMATES=parmest ;
RUN ;
```

In addition to the responder analysis, a cumulative distribution function (CDF) will be plotted for the 3 treatment groups, where the horizontal axis is the change from baseline in eosinophil count (x), ranging from the smallest (negative value meaning reduction) to the largest (positive value meaning increase) observed in the trial, and the vertical axis is the percentage of patients whose eosinophil count is ≤x cells/HPF.

7.11 Analysis of Secondary Efficacy Endpoints

A cumulative distribution function (CDF) plot will be generated for the 3 treatment groups for the percent changes from baseline in the TSS scores averaged over the 14 daily scores starting with the day of the last dose to the day before the end of the study biopsy. (See Section 5.2 for detail of the calculation.)

7.11.1 Treatment Responder at End of Study Treatment

Proportion of patients with a >30% reduction in TSS combined with a >75% reduction in eosinophils in the gastric and/or duodenal mucosa will be analyzed using the logistic regression model similar to Section 7.10.2 Sensivity Analysis. The calculation of the TSS score is found in Section 5.2 1st Secondary Endpoint.

As an exploratory analysis, the analysis of the treatment responder will be repeated for select subgroups (Section 6.9) such as EG, EGE, and EG + EGE. For each subgroup, separate logistic regression analysis will be performed similar to the sensitivity analysis for the primary endpoint of Section 7.10.3. In the analysis, two active dose groups will be combined for the comparison to the placebo group.

7.11.2 Patient Reported Outcome – TSS at End of Study Treatment

The average of TSS score at the end of study treatment is calculated as per the 1st Secondary Endpoint (Section 5.2). ANCOVA will be applied with treatment as factor, and baseline value and randomization stratum as covariates. The order of the analysis follows the hierarchy definded in Section 6.8.

7.12 Analysis of Exploratory Endpoints

- Change in [redacted] will be analyzed using [redacted] as described below. Only the [redacted] collected prior to study drug dosing will be included in the model. The [redacted] model includes treatment, week, treatment-by-week interaction as fixed factors, and baseline as covariates. Subject will be the repeated measure factor. The covariance matrix for the repeated measurements will take the form of Toeplitz (TOEP). If the computation does not converge, it will be reduced to the first order autoregressive [AR(1)] followed by compound symmetry (CS). The weekly change scores from Week 1 up to Week 14 will be included in the model.
- Change from baseline in the [redacted] scores averaged over the 14 daily scores starting with the day of the last dose to the day before the end of study biopsy. (See 1st Secondary Endpoint for the calculation of average.) For patients whose biopsy is collected prior to Day 99 due to early discontinuation, the average of the last 14 days of

scores recorded for that patient will be used for the analysis will be analyzed using the same method as for the [redacted] and TSS scores.

- The average of [redacted] scores at the end of study treatment is calculated as per the 1st Secondary Endpoint (Section 5.2). [redacted] will be applied with treatment as factor, and baseline value and randomization stratum as covariates.
- Percent Change in the number of [redacted] in patients with [redacted] will be analyzed using the same method as for the primary efficacy endpoint (see Section 7.10.1).
- Proportions of EG, EGE, and EoE patients with average [redacted] per HPF (EG and EGE) or [redacted] per HPF (EoE) from [redacted] will be analyzed using the same method as the sensitivity analysis for the primary efficacy endpoint (see Section 7.10.3).
- [redacted] (respectively) will be summarized at baseline and Week 14 (Day 99).
- Changes in the number of [redacted] separately in [redacted] may be analyzed using [redacted] similarly to the primary endpoint analysis if sample sizes allow.
- Change from baseline in the scoring of [redacted] will be summarized descriptively using mean, SD, and median. Individual assessments will be summarized using frequency tables
- Changes from baseline in the [redacted] domain and summary scores will be analyzed similarly to the PRO TSS scores. Instead of using the weekly score, the analysis will be based on the [redacted] item scores collected at each visit. The computation of the domain scores and summary scores will be provided by the Optum PRO CoRE software.
- Change from baseline in the [redacted] for EoE patients will be summarized.
- Percent changes from baseline in [redacted] for averages of Weeks 13-14, 11-14, and Weeks 9-14, and separately for each individual week will be summarized. Baseline for each of the symptom scores is defined the average of all scores for that symptom prior to the first dose of the study drug. The postbaseline weekly [redacted] and their percent changes will be summarized for each treatment group everyweek. The weekly percent changes will be analyzed using the [redacted] model as described in the analysis for the peripheral eosinophil counts. The comparison between the active dose and placebo

groups for averages of Weeks 13-14, 11-14, and 9-14 will be based on the averages of the least squares means for the corresponding weeks using simple contrasts. The comparison for each individual week will be carried out similarly. P-values and confidence intervals will be presented without multiplicity adjustment.

```
PROC MIXED DATA=XXXX ;
    CLASS TRTP USUBJID WEEK;
    MODEL PCHG = BASE TRTP WEEK TRTP*WEEK / DDFM=KR ;
    REPEATED WEEK / SUBJECT=USUBJID(TRTP) TYPE=TOEP ;
    ESTIMATE "GRP1-GRP3 @ W9-14Avg" TRTP  6  0 -6
        TRTP* WEEK  0  0  0  0  0  0  0  0  1  1  1  1  1  1
                    0  0  0  0  0  0  0  0  0  0  0  0  0  0
                    0  0  0  0  0  0  0  0 -1 -1 -1 -1 -1 -1
                    / CL DIVISOR=6;
    ESTIMATE "GRP2-GRP3 @ W13-14Avg" TRTP   0 2 -2
        TRTP* WEEK  0  0  0  0  0  0  0  0  0  0  0  0  0  0
                    0  0  0  0  0  0  0  0  0  0  0  0  1  1
                    0  0  0  0  0  0  0  0  0  0  0  0 -1 -1
                    / CL DIVISOR=2;
    ESTIMATE "GRP1-GRP3 @W1" TRTP  1 0 -1
        TRTP* WEEK  1  0  0  0  0  0  0  0  0  0  0  0  0  0
                    0  0  0  0  0  0  0  0  0  0  0  0  0  0
                   -1  0  0  0  0  0  0  0  0  0  0  0  0  0
                    / CL;
RUN ;
```

- Changes from baseline in the [redacted] for averages of Weeks 13-14, 11-14 and Weeks 9-14 and separately for each individual week will be analyzed in the same way as for the percent change from baseline.
- Change from baseline in [redacted] will be analyzed using MMRM similarly as described for and [redacted] and TSS scores.
- [redacted] will be summarized at baseline and Week 14 using geometric mean, coefficient of variation, median, and minimum and maximum.
- Subject counts at each [redacted] at Day 99 will be tabulated.

7.13 Analysis of Pharmacokinetic Endpoint

Serum concentrations of AK002 will be summarized for each treatment group by study visit.

7.14 Safety Analyses

7.14.1 Adverse Events

Safety assessments will be based mainly on the nature, frequency, relationship, and severity of adverse events (AEs). AEs will be coded by primary system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. The treatment-emergent adverse events (TEAEs) will be summarized by the number and percentage (n and %) of subjects in each SOC and PT. For summaries by relationship to study drug, "possibly related" will be combined with "related", and "unlikely/remotely related" will be combined with "not related." When multiple AEs are reported with the same PT, the AE of the strongest relation will be included in summary by relationship, and the AE of the most severe grade will be included in the summary by severity table.

The following AE incidence tables will be presented.

- Overview of TEAEs to include
  - Number (%) of patients who reported at least one TEAE
  - Number (%) of patients who reported at least one treatment-related TEAE
  - Number (%) of patients who reported at least one severe TEAE
  - 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 died on study
- TEAEs by PT sorted by decreasing order of subject incidence in the combined treatment group
- TEAEs by SOC and PT in alphabetical order
- TEAEs by SOC, PT, and maximum severity
- TEAEs by SOC, PT, and strongest relationship to study drug
- TEAEs leading to withdrawal by SOC and PT, if warranted by sample size
- Serious TEAEs by SOC and PT, if warranted by sample size

All AEs will be listed with onset/stop day, relationship to study drug, severity, action taken, and outcome. Pertinent subject information including treatment group and demographics will also be included.

Separate listings will be provided for TEAEs leading to study discontinuation, TEAEs of special interest, and Treatment-emergent serious AEs (TESAEs).

7.14.2 Laboratory Test

Laboratory data will be summarized by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges). For quantitative laboratory parameters, both actual values and change from baseline values will be summarized.

Shift tables will be presented, in which, lab test results at baseline and post-baseline will be classified into below (<LLN), within (≥LLN and ≤ULN), and above (>ULN) normal ranges. Subject incidences (n and %) will be presented for the shift from baseline to the post-baseline visits.

Note the summary and shift tables will only use the planned/scheduled tests. However, both scheduled and unscheduled/repeat tests will be included in the data listing.

A complete laboratory data listing, including hematology, biochemistry, urinalysis, and Anti-Drug-Antibodies (ADA) will be provided for all subjects.

7.14.3 Vital Signs, Height and Weight, and Other Safety Measures

Vital signs will be summarized by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) for each scheduled visit and time point. A data listing will include vital signs from all visits.

7.14.4 Physical Examination

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

7.14.5 Analysis of Anti-Drug Antibody

Number (%) of subjects who are ADA positive at any time after receiving study drug and number (%) of subjects who are ADA positive at the end of study will be cross-tabulated by their ADA status at predose.

8. Validation

The Clinical Operations and Data Management at Allakos will work with EDC/Data Management (DM) vendor to ensure that the data collected for the study are of the highest quality possible. The study monitor will be responsible for reviewing and verifying the accuracy of the data recorded on the electronic case report forms (eCRFs) directly from source documents at the investigative site. The DM vendor will be responsible for performing edit checks and reviewing all data entered into the electronic database to identify discrepant and/or inconsistent values and to send queries to the clinical sites. The Investigator will be responsible for answering queries about discrepant data and providing electronic signatures to confirm data integrity.

The programming of Tables, Listings and Figures (TLFs) based on the clinical data is outsourced. Allakos seeks to ensure the quality of the reports provided by the CRO in the form of TLFs passing a rigorous validation process as follows:

- Derived datasets will be independently reprogrammed by a second programmer. The separate datasets produced by the 2 programmers must match 100%.
- Tables will be independently reprogrammed by a second programmer and the results from both programs must match.
- Figures will be checked for consistency against corresponding tables and listings, or independently reprogrammed if there are no corresponding tables or listings.
- Listings will be checked for consistency against corresponding tables, figures, and derived datasets.

All post hoc analysis, if accepted for inclusion in the study report, will follow the same quality process as stated above. The entire set of TLFs will be checked for completeness and consistency prior to its delivery to Allakos.

9. References

International Council for Harmonisation (ICH). Guideline for industry E3, structure and content of clinical study reports, July 1996.