

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

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## Statistical Analysis Plan for Protocol AK002-021

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

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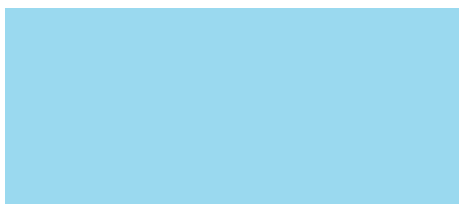
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## Table of Contents

<b>Statistical Analysis Plan for Protocol AK002-021.....</b>	<b>1</b>
<b>Signature Page.....</b>	<b>2</b>
<b>Table of Contents .....</b>	<b>3</b>
List of In-Text Tables .....	7
List of Abbreviations.....	8
<b>Revision History .....</b>	<b>11</b>
<b>1. Introduction .....</b>	<b>12</b>
<b>2. Study Objectives .....</b>	<b>12</b>
2.1 Primary Objective – Primary Endpoints.....	12
2.2 Secondary Objectives – Secondary Endpoints .....	13
2.3 Exploratory Objectives – Exploratory Endpoints.....	13
2.4 Safety Objectives – Safety Endpoints .....	13
<b>3. Study Design.....</b>	<b>14</b>
3.1 General Description.....	14
3.2 Study Treatment .....	21
3.2.1 Treatment, Dose, and Mode of Administration.....	21
3.2.2 Duration of Study .....	21
3.2.3 Methods of Assigning Subjects to Treatment Group .....	21
3.3 Blinding .....	21
3.4 Hypotheses .....	21
3.5 Determination of Sample Size.....	22
<b>4. Definitions .....</b>	<b>22</b>
4.1 Terminology and Definitions .....	22
4.2 Target of Estimation .....	23

4.2.1	Population Targeted by the Scientific Question .....	24
4.2.2	Variables of Interest (or Endpoint) to be Obtained for Each Subject that is Required to Address the Scientific Question .....	24
4.2.3	Treatment.....	25
4.2.4	Intercurrent Events .....	25
4.2.5	Strategy for Handling Intercurrent Events .....	25
4.2.6	Summary Measure of the Estimand .....	25
<b>5.</b>	<b>Statistical Methods .....</b>	<b>25</b>
5.1	General Methodology .....	25
5.2	Visit Window and Unscheduled Assessments .....	27
5.3	Adjustment for Covariates.....	29
5.4	Handling of Dropouts, Missing Data, and Data Discrepancies.....	29
5.4.1	Missing Duodenal Tissue Eosinophil Count at Week 24.....	29
5.4.2	Missing Daily PRO Scores at Weeks 23–24 .....	29
5.4.3	Missing or Partial Dates of Adverse Events or Concomitant Medications ...	30
5.5	Interim Analysis .....	31
5.6	Timing of Data Analyses.....	31
5.7	Multicenter Study .....	31
5.8	Multiple Comparisons/Multiplicity Adjustment .....	32
5.9	Examination of Subgroups .....	32
<b>6.</b>	<b>Statistical Analysis.....</b>	<b>33</b>
6.1	Analysis Populations .....	33
6.1.1	Safety Population.....	33
6.1.2	Intent-to-Treat Population .....	33
6.1.3	Modified Intent-to-Treat Population .....	33
6.1.4	Per Protocol Analysis Population.....	33

6.1.5	Primary Analysis Population.....	33
6.2	Disposition of Subjects.....	34
6.3	Protocol Deviations .....	35
6.4	Demographics and Baseline Subject Characteristics .....	35
6.5	Baseline Disease Characteristics .....	35
6.6	Medical History .....	35
6.7	Electrocardiogram .....	35
6.8	Pregnancy Test .....	36
6.9	Baseline Diet .....	36
6.10	Treatments .....	36
6.10.1	Treatment Compliance and Extent of Exposure.....	36
6.10.2	Prior, Concomitant, and Newly Initiated Medications.....	36
6.11	Analysis of Primary Efficacy Endpoints .....	37
6.11.1	Analysis of the First Co-Primary Endpoint.....	37
6.11.2	Sensitivity Analysis of the First Co-Primary Endpoint.....	38
6.11.3	Subgroup Analysis of the First Co-primary Endpoint.....	38
6.11.4	Analysis of the Second Co-Primary Endpoint.....	38
6.11.5	Sensitivity Analyses of the Second Co-Primary Endpoint.....	39
6.11.6	Supplementary Analyses .....	41
6.12	Analysis of Secondary Efficacy Endpoints .....	41
6.12.1	Change in Tissue Eosinophil Count .....	41
6.12.2	Proportion of Subjects Achieving Peak Duodenal Intraepithelial Eosinophil Count of $\leq 1$ Cell/hpf.....	41
6.12.3	Proportion of Treatment Responders.....	42
6.12.4	Proportion of Subjects with $\geq 50\%$ Reduction and $\geq 70\%$ Reduction in TSS from Baseline to Weeks 23–24.....	42
6.12.5	Change in Weekly TSS Over Time .....	42

6.13	Analysis of Exploratory Endpoints .....	42
6.13.1	Change in CCI .....	42
6.13.2	Change in CCI .....	42
6.13.3	Change in CCI .....	42
6.13.4	Change in CCI CCI .....	43
6.13.5	CCI .....	
6.13.6	CCI .....	
6.14	Analysis of Pharmacokinetic Endpoint .....	44
6.15	Safety Analyses .....	44
6.15.1	Adverse Events .....	44
6.15.2	Laboratory Test .....	45
6.15.3	Vital Signs, Height and Weight, and Other Safety Measures .....	46
6.15.4	Electrocardiogram .....	46
6.15.5	Physical Examination .....	46
6.15.6	Analysis of Anti-Drug Antibody .....	46
7.	Validation .....	46
8.	References .....	47
9.	Appendices .....	48
9.1	Appendix 1: Effect of Missing Data on the Weekly Mean of TSS .....	49
9.2	Appendix 2: Intercurrent Events .....	51
9.3	Appendix 3: List of Tables, Figures, and Listings .....	53
9.4	Appendix 4: Example SAS Codes .....	63

**List of In-Text Tables**

Table 1	Schedule of Assessments .....	16
Table 2	Terminology and Definitions .....	22
Table 3	Analysis Window Rules for CCI .....	27
Table 4	Analysis Window Rules for Vital Sign and Laboratory Tests.....	28
Table 5	Analysis Window Rules for PK Concentration and ADA.....	28
Table 6	Analysis Window Rules for Blood Histamine and Urinalysis.....	29
Table 7	Standard Errors for the Mean Weekly TSS Diaries by Number of Daily Diaries Missing Averaged over 500 Simulations .....	50



## List of Abbreviations

ADA	Anti-drug antibody
ADaM	Analysis Data Model T
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical (Classification System)
BLOQ	Below limit of quantification
BMI	Body mass index
CBC	Complete blood count
CDISC	Clinical Data Interchange Standards Consortium
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical study report
DM	Data management
eCDF	empirical cumulative distribution function
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture (system)
EG	Eosinophilic gastritis
EGD	Esophago-gastro-duodenoscopy
EGE	Eosinophilic gastroenteritis
EoD	Eosinophilic duodenitis
EoE	Eosinophilic esophagitis
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
hpf	High power field
ICE	Intercurrent events
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IRT	Interactive Response Technology
ITT	Intent-to-treat (population)

IV	Intravenous
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LSM	Least squares mean
MAR	Missing at random
MCAR	Missing completely at random
MCMC	Markov Chain Monte Carlo (method)
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation(s)
MITT	Modified intent-to-treat (population)
MMRM	Mixed Model for Repeated Measures
MNAR	Missing not at Random
p-value	Probability value
PD	Pharmacodynamics
PE	Physical examination
CCI	
CCI	
PK	Pharmacokinetic(s)
PP	Per protocol (population)
PPI	Proton pump inhibitor(s)
PRO	Patient-reported outcome
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical analysis system
SD	Standard deviation
SE	Standard error(s)
SDTM	Study Data Tabulation Model
CCI	
SOC	System organ class
TEAE	Treatment-emergent adverse event(s)
TEAESI	Treatment-emergent adverse event(s) of special interest
TESAE	Treatment-emergent serious adverse event(s)
TLF	Tables, listings, and figures

TSS	Total Symptom Score
ULN	Upper limit of normal
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

**Revision History**

<b>Version Date</b>	<b>Version Number</b>	<b>Description</b>
<b>29 June 2022</b>	<b>1</b>	Initial document

## 1. Introduction

This statistical analysis plan (SAP) describes the rules and conventions to be used in the analysis and presentation of efficacy and safety of AK002 in subjects with moderate-to-severe eosinophilic duodenitis (EoD) who have an inadequate response with, lost response to, or were intolerant to standard therapies, as planned for the clinical protocol.

The SAP describes the data and variables to be summarized or analyzed, including specifications of the analytical methods to be performed. This SAP supersedes the statistical analysis methods described in the clinical protocol except for the standard pharmacokinetic (PK) data analyses. 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). The SAP is based on Clinical Study Protocol AK002-021 Amendment 2, dated 16 June 2022, and the associated electronic case report forms (eCRF).

## 2. Study Objectives

### 2.1 Primary Objective – Primary Endpoints

The primary objectives of the study are to evaluate the efficacy and safety of 6 doses of AK002 in subjects with moderate to severe EoD when compared with placebo.

Efficacy will be evaluated by 2 co-primary endpoints:

- 1) First co-primary endpoint- Proportion of Tissue Eosinophil Responders at Week 24:  
A responder is a subject achieving a mean duodenal eosinophil count  $\leq 15$  cells/hpf in 3 highest duodenal hpf
- 2) Second co-primary endpoint- Change in TSS from baseline to Weeks 23–24 as measured by the Patient Reported Outcome (PRO) questionnaire.

The PRO Total Symptom Score (TSS) is comprised of the following 6 symptoms:

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

## 2.2 Secondary Objectives – Secondary Endpoints

The secondary objectives are to characterize further the efficacy of AK002 in subjects with EoD as measured by:

- Percent change in tissue eosinophils from baseline to Week 24
- Proportion of subjects achieving mean eosinophil count  $\leq 1$  cell/hpf in 3 highest duodenal hpf at Week 24
- Proportion of treatment responders at Weeks 23- 24. Responder is defined as  $>30\%$  improvement in TSS symptom score **and** mean eosinophil count  $\leq 15$  cells/hpf in 3 highest duodenal hpf
- Proportion of subjects who achieve  $\geq 50\%$  reduction in TSS from baseline to Weeks 23–24
- Proportion of subjects who achieve  $\geq 70\%$  reduction in TSS from baseline to Weeks 23–24
- Percent change in weekly TSS over time

## 2.3 Exploratory Objectives – Exploratory Endpoints

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

- Change from baseline in CCI [REDACTED] over time
- Changes in CCI [REDACTED] from baseline compared to post-treatment in the CCI [REDACTED]  
[REDACTED]
- Change from baseline in CCI [REDACTED] over time
- Change from baseline in CCI [REDACTED] over time

## 2.4 Safety Objectives – Safety Endpoints

The safety objective of the study is to evaluate the study drug safety profile using the following safety endpoints:

- Treatment emergent adverse events (TEAE) including severity, relationship to study treatment, action taken, and outcome, serious adverse events (SAE) and adverse events (AE) leading to study drug withdrawal
- Anti-drug (AK002) antibody (ADA)
- Blood chemistry
- Hematology

- Urinalysis
- Physical examination
- Changes in vital signs
- Changes in concomitant medication use due to AE

### 3. Study Design

#### 3.1 General Description

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

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

Subjects who have signed the informed consent form (ICF) will be screened during 21-45 days prior to Study Day 1.

The study will be carried out as follows:

- A screening period of 21–45 days with baseline evaluations for study eligibility, including active symptoms of disease (gathered by the patient reported outcome [PRO] questionnaire completed during screening) and EGD and colonoscopy (performed on the same day) with biopsy.
- Stool antigen test for *Helicobacter pylori* (*H. pylori*) will be assessed during screening to confirm no active *H. pylori* infection exists. If *H. pylori* is detected in tissue biopsies by the central pathologist, the patient should be excluded from the trial.
- If subjects meet histology and symptom eligibility criteria, they will be randomized after being stratified by the highest weekly TSS of disease activity recorded during the screening period ( $<28$  or  $\geq 28$  strata). The interactive response technology (IRT) will randomly assign subjects 1:1 to receive AK002 or placebo.
- Pre-study medications and dietary restrictions will remain unchanged throughout the study. Systemic or topical steroids above 10 mg prednisone will not be allowed except as a premedication prior to the first infusion only or due to unforeseen medical circumstances where it is deemed to be medically necessary to treat an unrelated medical condition or to treat an IRR that occurs during infusion.

- Eligible subjects will receive the first dose of placebo or AK002 (3 mg/kg) on Day 1 with premedication of 80 mg oral prednisone 12–24 hours prior to the start of the infusion.
- If the study drug is well tolerated (no stopping rules being met), subjects will receive additional doses of placebo or AK002 (3 mg/kg) on Days 29, 57, 85, 113, and 141. With the exception of Day 1, steroid premedication will only be allowed with the written approval of the Medical Monitor.
- Subjects will remain at the site for at least 1 hour of observation following the end of the infusion.
- A repeat EGD with biopsy will be performed on Day 169 ( $\pm 3$ ) or 28 ( $\pm 3$ ) days after last dose of study drug if subject is terminated early (between the Day 29 visit and the Day 169 visit).
- Daily administration of the PRO questionnaire (including additional questions) throughout the study and the follow-up period for all patients.
- Patients will rate their impression of disease severity CCI and disease improvement CCI at specified time points during the study.
- Patients will be prompted to answer additional questions about dysphagia and constipation on a daily basis during screening and throughout the study. These will be completed following the PRO questionnaire.
- Follow-up will occur for 84 ( $\pm 3$ ) days after the last dose unless subjects decide to enter the long-term, open-label extension (OLE) of the study. Follow-up visits for subjects opting not to enter the extension study will occur on Days 176 ( $\pm 3$ ), 197 ( $\pm 3$ ), and 225 ( $\pm 3$ ).
- Patients who receive all 6 doses of study drug have the option to receive AK002 by entering into the OLE period of the study if all eligibility criteria for the OLE period are satisfied. Patients who enter the OLE period of the study may begin the extension dosing 1 day after completing the Day 176 visit of this protocol. Open-label extension patients will not complete the Day 197 or Day 225 procedures under the double-blind period of the study.
- Eligible patients who choose to participate in the OLE period will begin following the OLE Schedule of Assessments (SOA) after completing the Day 176 double-blind period procedures and will receive the first dose of open-label AK002 approximately 1 week after Day 169 (on Day 177).
- Total study duration is approximately 35–37 weeks. For subjects entering the OLE period of the study, the total study duration is approximately an additional 28–30 weeks.

The overall schedule of procedures and assessments are presented in [Table 1](#).



**Table 1 Schedule of Assessments**

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

**Table 1 Schedule of Assessments cont.**

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

**Table 1 Notes**

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

- 1) Baseline screening visit can occur over several days within the screening period. Day 1 can begin as soon as eligibility criteria are met.
- 2) At screening, height (in cm) and weight (in kg) will be recorded. Body weight will also be measured on Days 1, 29, 57, 85, 113, 141, and on follow-up Days 176, 197 and 225 or 28,56, and 84 days after last dose, if ET. Current body weight or body weight from 1 day prior will be used to calculate the amount of AK002/placebo to be mixed with NaCl for the appropriate dose to be administered on each infusion day.
- 3) Vital signs will be measured at screening, Days 176, 197, and 225 or 28,56 and 84 days after last dose if ET and on all dosing days: within 30 minutes predose, 15 (±5) minutes after the start of study drug infusion, within 15 minutes following the end of infusion and just prior to discharge. Additional vital signs measurements may be collected at the Investigator's discretion if an IRR occurs. Vital signs including systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate will be measured after the patient has been at rest for ≥5 minutes and before any blood draws have been obtained (unless collected for an IRR).
- 4) A 10-lead or 12-lead ECG will be obtained at screening before any blood is drawn and after the patient has been in the appropriate position for ≥5 minutes.
- 5) A complete physical examination will be performed by either the Investigator or designee and include the following body system or organ assessments: skin; head, eyes, ears, nose and throat; thyroid; lungs; cardiovascular; abdomen; extremities; lymph nodes; and a brief neurological examination.
- 6) A symptom-directed physical exam (including assessment of possible infusion site reactions) will be performed by the Investigator or designee, as needed, if any symptoms are reported.
- 7) A baseline diet assessment (Protocol Appendix 3) will be performed using standardized questions. Eating patterns, food avoidance behaviors, and confirmed allergies will be captured.
- 8) A baseline diet compliance check will be performed at every study visit, except as noted above, and any variances from the baseline diet documented. Patients should maintain the baseline diet throughout the study.
- 9) Fecal collection kits for ova and parasite test will be provided to patients at screening. Collection kits should be returned to the clinical site within 1 day of collection. Negative results must be available prior to randomization.
- 10) Activate PRO questionnaire and provide patient with unique username and password. PRO questionnaire should be activated for all patients on screening Day 1.
- 11) PRO should be completed around the same time each day. Prior to enrollment, the PRO weekly averages of abdominal pain, nausea, and diarrhea over the screening period will be calculated and used to assess eligibility. Weekly average Total Symptom Score (TSS6) will be calculated for eligibility and stratification. Patients will also complete an additional question each about dysphagia and constipation daily during the screening period and throughout the study. The additional questions will be completed following the PRO questionnaire.

**Table 1 Notes cont.**

- 12) EGD + colonoscopy with biopsy (performed on the same day whenever possible) will include specimens from the gastric mucosa, duodenum, colon and esophagus (as applicable). Specimens will be processed by the central laboratory. See the Histology Manual for collection, processing, and shipping details. The specimens will be evaluated by a central pathology reader. Additional biopsies will be collected for exploratory analysis. Prior EGD and colonoscopy biopsy samples may be used for eligibility as long as they were performed within 45 days of the AK002-021 screening window for the AK002-021 study and were performed and centrally assessed using the same criteria as for the AK002-021 study, and there were no changes to EoD therapy following the EGD.
- 13) The **CCI** is to be completed electronically by patient, in clinic, prior to any blood draw, physical exam, or vital sign measurements.
- 14) See Protocol Appendix 5 for biopsy assessments. The post-treatment EGD + colonoscopy and biopsy assessments will be performed on Day 169 ( $\pm 3$ ) or 28 ( $\pm 3$ ) days after last dose of study drug if ET. Post-treatment EGD + colonoscopy biopsy results will be blinded to the site.
- 15) Blood for baseline chemistry, including hCG and FSH, will be collected during the screening period. Only patients of childbearing potential and post-menopausal women are required to have hCG and FSH testing completed.
- 16) Blood for serology testing will be collected during screening and will include HBsAg, hepatitis C antibody, anti-HBc, and HIV, as well as Strongyloides stercoralis.
- 17) Blood samples for total serum IgE will be collected during screening and on Day 176 or 35 ( $\pm 3$ ) days after last dose of study drug, if ET.
- 18) Stratification based on TSS of  $<28$  or  $\geq 28$  will occur. Randomization and stratification will be conducted through the IRT system.
- 19) Premedication with 80 mg oral prednisone or approved alternative is required 12–24 hours prior to the first infusion. Premedication prior to the start of the second through sixth infusions will only be administered with the prior written approval of the Medical Monitor.
- 20) Study drug will be administered as a single peripheral intravenous infusion over at least 4 hours for Dose 1 and at least 1 hour for subsequent doses. Refer to the Pharmacy Manual.
- 21) Blood for CBC with differential, including absolute blood eosinophil count, will be obtained once during screening, Day 8, Day 15, and once during each follow-up visit or ET visit, as well as twice during dosing days just prior to each infusion and 1 hour ( $\pm 15$  minutes) after the end of each infusion. All differential blood counts from Day 1 (postdose) through the end of the patient's participation will be blinded to the Sponsor and the site. An unscheduled CBC may be collected at the request of the Safety Monitor.
- 22) Blood for chemistry will be obtained once during screening and once during each follow-up visit or ET visit as well as predose on dosing days.
- 23) Blood for PK will be obtained predose on dosing Days 29, 57, 85, 113, and 141, as well as during screening and on Days 8, 15, 169, 176, 197, and 225 or 28, 35, 56, and 84 ( $\pm 3$ ) days after last dose of study drug if ET.
- 24) Blood for ADA will be collected at screening and predose on dosing Days 1, 29, 57, and 85, as well as on Day 169 and 225 or 28 ( $\pm 3$ ) and 84 ( $\pm 3$ ) days after last dose of study drug if ET. The ADA sample will also be collected any time an immunogenicity-related AE occurs.
- 25) Urine for standard urinalysis will be obtained at screening, predose on dosing Day 29, ET, and symptom based, as necessary.

**Table 1 Notes cont.**

- 26) Urine will be collected for dipstick pregnancy test on all infusion days and on Day 176 and Day 197 or 35 and 56 ( $\pm 3$ ) days after last dose of study drug, for all patients of childbearing potential. Test kits will be supplied by the central laboratory. Tests will be completed on site and evaluated prior to each infusion.
- 27) The capture of non-serious AE and AESI will begin after the first dose of study drug has occurred.
- 28) The reporting of SAE occurring after signing the informed consent and prior to the first infusion will be limited to those that relate to screening procedures. The capture of all SAE and AE that are not related to screening procedures will begin at the time of first infusion of study drug. For patients participating in the OLE period, AE will be assessed and recorded in the CRF of the AK002-021 double-blind treatment period database up until the start of the first open-label infusion, after the Day 176 visit. The AE will be recorded in the CRF of the AK002-021 OLE period database beginning with the start of the first open-label infusion after Day 176.
- 29) Patients who continue in the OLE period of the study will complete the procedures for Day 176 and may begin open-label dosing in the OLE period of the study, if eligible, 1 day after completion of the Day 176 visit. In this case, patients will not complete the Day 197 or Day 225 procedures under the double-blind period of the study.
- 30) The ET visits should be conducted 28, 35, 56, and 84 ( $\pm 3$ ) days after last dose of study drug or prior to this, if necessary, to ensure compliance with the visit. If only 1 ET visit is possible, EGD + colonoscopy and end-of-study procedures may occur on the same day. If the end-of-study visit occurs more than 35 days after last dose of study drug, then perform the visit as soon as possible. The procedures listed under the 28-day and 35-day post-study drug visit will be conducted unless otherwise directed by the Medical Monitor. For patients participating in the OLE period, AE and concomitant medications should be collected and recorded in the AK002-021 double-blind treatment period database up until the start of the first open-label infusion after the Day 176 visit. This includes prednisone premedication administered after the Day 176 visit of the OLE period, which should be recorded in the Concomitant Medications CRF of both the AK002-021 double-blind treatment period database and the AK002-021 OLE period database.
- 31) The final hematology assessment for the double-blind period of the study **must** be collected **prior to** the patient taking prednisone premedication for the first dose of the OLE period. Therefore, dosing in OLE must take place at least 1 day after completion of the Day 176.
- 32) Stool antigen test for *H. pylori* will be obtained to confirm no existing active *H. pylori* infection is present. Fecal collection fecal kits (same container as for ova and parasite testing) should be returned to the clinical site within 1 day of collection. Negative results must be available prior to randomization. If *H. pylori* is detected in tissue biopsies by the central pathologist, the patient should be excluded from the trial. In case of a positive test, the patient must be screen failed. After *H. pylori* treatment and an additional 6 weeks later, patient may be reconsented and will receive a new patient number.

## 3.2 Study Treatment

### 3.2.1 Treatment, Dose, and Mode of Administration

Subjects will be randomly assigned through the IRT system to an active 6 doses of AK002 at 3 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 on Days 1, 29 ( $\pm 3$ ), 57 ( $\pm 3$ ), 85 ( $\pm 3$ ), 113 ( $\pm 3$ ), and 141 ( $\pm 3$ ).

### 3.2.2 Duration of Study

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

- Screening phase: 21–45 days prior to study drug administration
- Treatment phase: 20 weeks
- Follow-up period: A follow-up period of 84 days ( $\pm 3$ ) after last dose of study drug.
- Patients who enter the OLE period of the study will participate in the double-blind period of Study AK002-021 for 26–32 weeks and will complete the study at least through the Day 176 visit.
- Patients who enter the OLE period prior to Day 197 will not complete the Day 197 visit or Day 225 visit of the double-blind study period but will instead follow the OLE schedule of events through Day 373.

### 3.2.3 Methods of Assigning Subjects to Treatment Group

Approximately 80 subjects with active EoD (without EG) will be stratified by baseline TSS. Subject will be randomized 1:1 to receive 1 of 2 dose regimens using stratified randomized blocks in a double-blind manner.

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

## 3.3 Blinding

This is a double-blind study. The identity of active and placebo treatments will not be known to Investigators, Sponsor (including safety monitor), research staff (including pharmacy), subjects, or the study monitor.

## 3.4 Hypotheses

The hypothesis to be tested in the study is that AK002 is different from placebo regarding the 2 co-primary efficacy endpoints of the proportion of subjects with tissue eosinophil response at Week 24 and the mean reduction from baseline in TSS at Weeks 23–24.

### 3.5 Determination of Sample Size

A total of approximately 80 subjects will be enrolled.

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

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

## 4. Definitions

### 4.1 Terminology and Definitions

**Table 2 Terminology and Definitions**

Terminology	Definition
Baseline	Baseline for non-daily assessment (e.g., laboratory tests and CCI) is defined as the non-missing value collected most recent to and before the time of the very first dose of study drug. This includes lab test collected on Day 1 Predose as an example. Baseline Total Symptom Score (TSS) will be the average of the weekly TSS collected in the last 2 weeks prior to the first dose. The day before and day of colonoscopy will be taken into consideration when computing baseline TSS.
Completer for the Study	Subjects who complete at least through the Day 176 visit if continuing to the OLE period of the study or Day 225 visit if not continuing to the OLE period of the study.
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.
Enrolled	Subject who is randomized to a treatment group.
Newly Initiated Medication	Newly initiated medication refers to any medication with a start date $\geq$ Study Day 1
Patient-Reported Outcome	The patient-reported outcome (PRO) questionnaire evaluates 8 different symptoms with 10 daily questions for intensity and frequency: <ul style="list-style-type: none"> <li>Abdominal pain intensity</li> <li>Nausea intensity</li> <li>Vomiting intensity</li> <li>Vomiting frequency</li> </ul>

**Table 2 Terminology and Definitions cont.**

Terminology	Definition
Patient-Reported Outcome cont.	<ul style="list-style-type: none"> <li>• Diarrhea intensity</li> <li>• Diarrhea frequency</li> <li>• Fullness before finishing a meal (Early satiety) intensity</li> <li>• Loss of appetite intensity</li> <li>• Bloating intensity</li> <li>• Abdominal cramping intensity</li> </ul> <p>Each intensity evaluation is scored on a scale of 0=none to 10=worst possible.</p>
Prior Medication	Medication collected on the Prior/Concomitant Medication CRF, with start date prior to Study Day 1.
PRO Total Symptom Score	Total symptom score (TSS) is the sum of 6 (abdominal pain, abdominal cramping, bloating, nausea, early satiety, and loss of appetite) weekly average symptom intensity scores.
Study Day	Study Day 1 is defined as the date on which a subject took the first dose of study drug. Other study days are defined relative to Study Day 1. For visits prior to the first dose of study drug, 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.
Study Drug	AK002 or placebo administered by IV infusion.
Study Week	Study Week for PRO analysis is defined as 7 days a week starting from the day of first dose (Day 1).
Tissue Eosinophil Responder in EoD	Mean duodenal eosinophil count $\leq 15$ cells/hpf in 3 highest duodenal hpf.
Treatment-emergent	Adverse events reported in the clinical database with a date of onset on or after the start date of the first dose of the study drug.
Treatment Responder	Subject with $>30\%$ improvement in TSS from baseline and mean eosinophil count $\leq 15$ cells/hpf in 3 highest duodenal hpf.

## 4.2 Target of Estimation

The estimand (target of estimation) for Protocol AK002-020 is:

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

The sections below describe the attributes of the estimand consistent with the ICH E9 (R1) Addendum ([FDA, 2021](#)).



#### 4.2.1 Population Targeted by the Scientific Question

The population targeted by the scientific question is defined via the inclusion and exclusion criteria as part of the study protocol. Subjects must have a histological diagnosis of EoD. A key aspect of eligibility is that subjects must have a weekly average score of abdominal pain, nausea, or diarrhea  $\geq 3$  on the PRO questionnaire (score from 0–10) for at least 2 weeks of screening and a weekly average TSS of  $\geq 10$  for at least 2 weeks of screening.

The protocol specifically excluded conditions including inflammatory bowel disease, other chronic inflammatory diseases in the colon (with the exception of eosinophilic colitis), celiac disease, achalasia, or esophageal surgery as these were identified at the time of study conception as potential confounders to interpretation of the degree of change in TSS based on overlap in symptomatology and several of the symptom-based components of the TSS PRO. The intent of this study criteria was as an exclusionary measure for any condition that may interfere with the interpretation of the assessment of efficacy based on the TSS instrument however the list of exclusionary conditions was not exhaustive and other concomitant conditions that could likewise confound interpretation and detection of a treatment effect may not have been fully appreciated (see exclusion criterion 7 and Appendix 5 in study protocol).

Subsequently, a supplementary analysis of data from a recent study, AK002-016, focused on identification of baseline characteristics which correlate with degree of change in TSS6 at Weeks 23-24. This examination identified eight variables (age, gender, duodenal eosinophil counts, diarrhea frequency, history of IBS, abdominal pain, esophageal eosinophils per hpf  $>6$ , and history of IBS in combination with diarrhea intensity  $\geq 3$ ) that most influenced the degree of change of the TSS endpoint. Two of the variables (esophageal eosinophils per hpf  $>6$ , and history of IBS in combination with diarrhea intensity  $\geq 3$ ) potentially reflect other disease states (IBS, GERD or even active EoE) that could potentially impact multiple symptom components of TSS6. To ensure these two variables do not compromise the capacity to detect the treatment effect with symptoms of EoD as measured by the TSS questionnaire, the primary comparison of AK002 vs placebo will be conducted on the Evaluable population defined as subjects who do not exhibit any of the following conditions at baseline:

1.  $>6$  eosinophils per hpf in at least one esophageal site.
2. Documented history of irritable bowel syndrome and baseline diarrhea intensity  $\geq 3$ .

#### 4.2.2 Variables of Interest (or Endpoint) to be Obtained for Each Subject that is Required to Address the Scientific Question

The co-primary endpoints to be obtained for each subject in this study to address the scientific question are [tissue eosinophil responders](#) (as defined in Table 2) at Week 24 and change in TSS from baseline to Weeks 23–24 as measured by the PRO questionnaire.

### 4.2.3 Treatment

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

### 4.2.4 Intercurrent Events

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

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

Further clarification and handling of ICE including prohibited/rescue medications is detailed in [Appendix 2](#).

### 4.2.5 Strategy for Handling Intercurrent Events

For the analysis of the study product estimand, tissue eosinophil values and TSS will be counted as non-responders for binary variables and set to missing for continuous outcomes from the point when an ICE occurs. The estimand will provide an answer to the question that is crucial to individual subjects:

“If I take this study medication as part of my treatment regimen, without adding any further medications that may impact the underlying disease or exit the study prematurely, what improvements in histology and PRO symptoms might be anticipated after 24 weeks?”

### 4.2.6 Summary Measure of the Estimand

- Percent (and 95% CI) of subjects having tissue eosinophil response at Week 24 in the AK002 and Placebo treatment groups and the absolute difference (and 95% CI) in the percent response between treatments.
- Least squares mean (LSM) (and standard error [SE]) of change from baseline to the average of Weeks 23–24 TSS and the between treatment difference in the AK002 and placebo treatment groups LSM. LSM and SE derived from mixed model repeated measures (MMRM) model.

## 5. Statistical Methods

### 5.1 General Methodology

All statistical analyses will be conducted using SAS v9.4 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 Technical 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 0 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 both treatment 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: Same number of decimal places as reported/collected
- Standard deviation: Same number of decimal places as reported/collected
- Percentiles, minimum, maximum: Same number of decimal places as reported/collected
- Odds Ratio: 2 decimal places
- Percentage: 1 decimal place generally, or 2 decimal places for <0.1%, or no decimal places for 0% and ≥100%
- P-value: 4 decimal places
- WBC: 2 decimal places as  $0.01 \times 10^9/L$
- Height/Weight/BMI: 1 decimal place

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 treatment group, subject ID, assessment name and date/time.

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.

## 5.2 Visit Window and Unscheduled Assessments

Data collected for study assessments provide information on the status of the subject at a given time point. These may provide biased results if the assessment is performed early or late. Therefore, assessments will be slotted into analysis windows to allow summaries to be performed for subjects with similar study drug exposure. The analysis window is constructed by the medians of 2 target study days of the adjacent planned visits.

**Table 3 Analysis Window Rules for CCI**

Visit Description	Window
Baseline	On or Prior to Day 1 Predose
Day 1	Predose on infusion Day 1
Day 29	Day 1 Postdose to Day 42
Day 57	Day 43 to Day 70
Day 85	Day 71 to Day 98
Day 113	Day 99 to Day 126
Day 141	Day 127 to Day 158
Day 176	Day 159 to Day 186
Day 197	Day 187 to End of Study

**Table 4 Analysis Window Rules for Vital Sign and Laboratory Tests**

<b>Visit Description</b>	<b>Window</b>
Baseline	On or Prior to Day 1 Predose
Day 1	Day 1 Postdose
Day 15	Day 2 to Day 22
Day 29	Day 23 to Day 42
Day 57	Day 43 to Day 70
Day 85	Day 71 to Day 98
Day 113	Day 99 to Day 126
Day 141	Day 127 to Day 158
Day 176	Day 159 to 186
Day 197	Day 187 to End of Study

**Table 5 Analysis Window Rules for PK Concentration and ADA**

<b>Visit Description</b>	<b>Window</b>
Baseline	On or Prior to Day 1 Predose
Day 8	Day 1 Postdose to Day 11
Day 15	Day 12 to Day 22
Day 29	Day 23 to Day 42
Day 57	Day 43 to Day 70
Day 85	Day 71 to Day 98
Day 113	Day 99 to Day 126
Day 141	Day 127 to Day 154
Day 169	Day 155 to Day 172
Day 176	Day 173 to Day 186
Day 197	Day 187 to Day 210
Day 225	Day 211 to End of Study

**Table 6 Analysis Window Rules for Blood Histamine and Urinalysis**

Visit Description	Window
Baseline	On or Prior to Day 1 Predose
Day 1	Predose on Day 1
Day 29	Day 1 Postdose to Day 42
Day 57	Day 43 to Day 70
Day 85	Day 71 to Day 98
Day 113	Day 99 to Day 126
Day 141	Day 127 to Day 158
Day 176	Day 159 to Day 186
Day 197	Day 187 to End of Study

In the event of multiple values from unscheduled or early termination assessments within a single analysis window, the value closest to the scheduled visit target study day will be used for analyses. If 2 values tie as closest to the time point (for example, 1 value is before and the other value is after the time point), then the later value will be selected. Data collected at all visits will be included in the data listings with visit presented as reported by the site.

### 5.3 Adjustment for Covariates

Efficacy analyses will be adjusted for baseline values and randomization stratum using ANCOVA, MMRM, or Cochran-Mantel-Haenszel tests, where applicable.

### 5.4 Handling of Dropouts, Missing Data, and Data Discrepancies

#### 5.4.1 Missing Duodenal Tissue Eosinophil Count at Week 24

Eosinophil counts will be set to missing if they are collected after subjects have experienced ICE. Subject with missing Week 24 tissue eosinophil count for any reason will be imputed with the eosinophil count collected from the postbaseline unscheduled visit prior to missing. If no eosinophil count is collected postbaseline, the subject will be considered treatment failure for tissue eosinophil response.

#### 5.4.2 Missing Daily PRO Scores at Weeks 23–24

PRO daily scores will be set to missing if they are collected after subjects have experienced ICE. We note that the day before and day of colonoscopy will be taken into consideration when computing baseline and Week 24 TSS scores. For the endpoints of change in the weekly average of PRO TSS, when  $\geq 4$  of 7 daily scores are available, the weekly average score will be calculated using the available daily scores. (See [Appendix 1](#) for justification of allowing weekly

average being calculated from  $\geq 4$  daily scores.) This calculation implies the missing daily scores are the same as the mean of the non-missing daily scores. When  $\geq 4$  daily scores are missing, the weekly score will be set to missing. For the calculation of the average PRO TSS over Weeks 23–24, if  $\geq 1$  weekly score is missing, the biweekly average of Weeks 23–24 will be considered missing.

Missing average of Weeks 23–24 TSS will be imputed using the Markov Chain Monte Carlo (MCMC) method. Baseline tissue eosinophil count and PRO TSS will be included along with the average biweekly PRO TSS (W01\_02, W03\_04, W05\_06, ..., W21\_22, W23\_24) in the multivariate distribution construction. The imputation will be carried out for each treatment group separately and will be executed multiple (50) times (MI). The purpose of MI is to account for the imputation variability in the parameter estimates. An example of the SAS code for this imputation follows.

```
proc mi data=TSS seed=1357986420 nimpute=50
out=TSS_IMPUTED ;
    by TRTMT ;
    mcmc chain=multiple impute=full initial=em nbiter=200 niter=100 ;
var B_EOS B_TSS TSS_W01_02 TSS_W03_04
... TSS_W21_22 TSS_W23_24 ;
run ;
```

After the imputation, the least squares mean (LSM) and standard error (SE) are derived from the conventional ANCOVA from each imputed data set.

These LSM and SE are synthesized to derive the imputation variability-adjusted LSM and SE for each treatment group and for the between treatment difference. These synthesized LSM and SE are then used in the hypothesis test for the between treatment difference. An example of the SAS code for the synthesized LSM comparisons between treatment is as follows.

```
ods output ParameterEstimates=LSMDIF ;
proc mianalyze data=DIFF alpha=0.05 ;
    modeleffects LSM ;
    stderr SE ;
run ;
```

### 5.4.3 Missing or Partial Dates of Adverse Events or Concomitant Medications

Adverse events with incomplete start or stop dates (i.e., either day or month is missing) will be considered treatment-emergent adverse events (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). Adverse

events with missing relationship to study drug will be included in the “Related” category for the summary tables and footnoted. Adverse events 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.

### **5.5 Interim Analysis**

No interim analysis is planned.

### **5.6 Timing of Data Analyses**

The database lock will occur after all subjects complete participation in the double-blind period of the study.

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

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

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

### **5.7 Multicenter Study**

The study will have approximately 35 sites. Analysis of site effect will be based on analysis centers. Analysis centers will be formed in such a way that there are sufficient subjects per



pooled analysis center for the assessment of study site effects. Pooling of study sites by geographic location is described below:

- **Analysis Center 1:** Massachusetts, Connecticut, Rhode Island, New York, New Jersey, Pennsylvania, District of Columbia, Maryland, Maine, Vermont, Delaware, and New Hampshire
- **Analysis Center 2:** Virginia, West Virginia, South Carolina, Georgia, Mississippi, Florida, Alabama, Louisiana
- **Analysis Center 3:** North Carolina, Tennessee, Ohio, Michigan, Indiana, Kentucky
- **Analysis Center 4:** South Dakota, Arkansas, Minnesota, Wisconsin, North Dakota, Illinois, Missouri, Iowa, Texas, Oklahoma, Kansas, Nebraska, Wyoming, Colorado
- **Analysis Center 5:** Utah, New Mexico, Arizona, California, Oregon, Washington, Idaho, Hawaii, Alaska, Montana, Nevada

### 5.8 Multiple Comparisons/Multiplicity Adjustment

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

Test each co-primary efficacy endpoint at 2-sided  $\alpha=0.05$  level.

- If  $p \leq 0.05$  for both co-primary endpoints, then reject the null hypothesis that AK002 is no different from placebo and accept the alternative hypothesis that AK002 is superior to placebo in reducing tissue eosinophil count and TSS score.
- If  $p \leq 0.05$  for both co-primary endpoints, the hypothesis tests for the secondary endpoints will proceed in the prespecified order.
- If  $p > 0.05$  for either co-primary endpoint, the null hypothesis is accepted. No hypothesis test will be performed for the secondary endpoints.
- The issue of multiplicity of secondary endpoints will be handled by statistical testing of these outcomes in a hierarchical fashion. The order of secondary endpoints is described in Section 2.2. If at any point during the analysis of the secondary endpoints, the statistical test is not significant at 2-sided  $\alpha=0.05$  level, the hypothesis testing procedure will stop. AK002 will be deemed superior to placebo for all endpoints prior to the stop.

### 5.9 Examination of Subgroups

Key endpoints will be summarized by subgroup to assess the consistency of the treatment effect across subgroups. Subgroups to be considered are:

- Gender (Male, Female)
- Age (<65, ≥65)
- Race (White, Non-White)
- IgE (<45, ≥45)

## **6. Statistical Analysis**

### **6.1 Analysis Populations**

The population of “all screened subjects” comprises subjects who signed the informed consent (ICF).

#### **6.1.1 Safety Population**

The safety population comprises randomized subjects who have received at least 1 dose of the study drug.

#### **6.1.2 Intent-to-Treat Population**

The intent-to-treat (ITT) population is defined as subjects who were randomized to treatment.

#### **6.1.3 Modified Intent-to-Treat Population**

The modified intent-to-treat (MITT) population is defined as subjects who were randomized and received at least 1 dose of the study drug.

#### **6.1.4 Per Protocol Analysis Population**

The per protocol (PP) population will include the Evaluable population (see Section 6.1.5) who have received at least 1 dose of study drug and did not have major protocol violations potentially interfering with the efficacy assessment. The PP exclusion criteria will be specified prior to the database lock and unblinding.

#### **6.1.5 Primary Analysis Population**

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

1. >6 eosinophils per hpf in at least one esophageal biopsy at baseline
  2. Documented history of irritable bowel syndrome and baseline diarrhea intensity  $\geq 3$ .
- The complement to the Evaluable population will be referred to as the Excluded population. It is worth remarking that for this study, if a subject has a history of concomitant EoE, or if

esophagus looks suspicious for EoE or other condition, or if patient is symptomatic on screening dysphagia question, quantified by a score of  $>3$  on the dysphagia question on at least 1 day during screening, then the following is undertaken:

- A set of 2 fragments is collected from the distal esophagus
  - A set of 2 fragments is collected from the mid-proximal esophagus
  - Up to 2 extra specimens may be collected if there are any additional areas of interest.
- A count of  $>6$  eosinophils per hpf in at least one esophageal site will be considered diagnostic of at least having esophageal eosinophilia for the purposes of the study and in cases where there is a history of EoE this could reflect active eosinophilic esophagitis although fulfillment of the diagnostic criteria for that condition may not be certain (see Appendix 5 for details).

Analysis will be conducted on the complement population, referred to as Excluded Population, and is planned as exploratory. In addition, for completeness purposes, analysis will be conducted on the mITT population to show what the study results would have been on all the subjects prior to removing those with confounding conditions outlined above.

## 6.2 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 both treatment groups combined. The primary reasons for study discontinuation will be included in the tabulation. The primary reasons may include, but are 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, MITT, and PP populations will be included in the table. A data listing for subject disposition will be presented for all enrolled subjects.

### 6.3 Protocol Deviations

Protocol deviations will include, but are not limited to

- Non-compliance with 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 who are excluded from the PP population will be listed with reasons for exclusion.

### 6.4 Demographics and Baseline Subject Characteristics

Descriptive statistics for subject characteristics and baseline values will be presented for all populations by treatment group and both treatment 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 Evaluable, Excluded, mITT, and PP populations.

### 6.5 Baseline Disease Characteristics

Baseline disease characteristics including demographics, weight, blood eosinophils ( $\geq 500$  cells/ $\mu$ L), IgE, IgE category ( $<45/\geq 45$ ), history of atopic dermatitis, functional GI symptoms, history of EG and/or EoD, duodenal eosinophils (per 3hpf in EoD), TSS total score at baseline, PRO symptom scores, and baseline elevated esophageal eosinophils histologic criteria will be included in the subject data listing.

### 6.6 Medical History

Subject incidence (n and %) of medical history (and current medical condition before signing the informed consent) will be tabulated by the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0) System Organ Class (SOC) and Preferred Term (PT).

### 6.7 Electrocardiogram

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

## **6.8 Pregnancy Test**

A listing of pregnancy test results will be provided.

## **6.9 Baseline Diet**

A listing of baseline and on-study diet assessment and compliance will be provided.

## **6.10 Treatments**

### **6.10.1 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 last dose minus the date of 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 that subjects received divided by 6 (i.e., total number of infusions expected)  $\times 100\%$ . 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.

### **6.10.2 Prior, Concomitant, and Newly Initiated 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; medications taken on or after Study Day 1 will be considered as concomitant medications; and newly initiated medication refers to any medication with a start date  $\geq$  Study Day 1. We note that a Prior Medication may also be a Concomitant Medication if the start date is prior to Study Day 1 and the end date is on/after Study Day 1. Medications will be coded using the WHO Drug Dictionary (WHODD March 2018 release) for PT and Anatomical Therapeutic Chemical (ATC) classification.

Medications will be tabulated separately based on the Safety population. The number (n and %) of subjects taking at least 1 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.

## 6.11 Analysis of Primary Efficacy Endpoints

To assist the data interpretation, all ICE will be listed with pertinent subject information (subject ID, date of last infusion, ICE start/stop day, nature of ICE (reason for treatment/study discontinuation if applicable, description of AE, description of prohibited/restricted medication), baseline tissue eosinophil count and TSS, and most recent tissue eosinophil count and 2-week average of TSS). A summary table will be created to present number of subjects (n, %) by treatment group:

- Subjects with any ICE
  - Subjects by ICE category

### 6.11.1 Analysis of the First Co-Primary Endpoint

The first co-primary endpoint will be analyzed using the imputed data set (Section 5.4.1). Fisher's exact test (primary analysis) will be conducted comparing AK002 with placebo for the proportion of tissue eosinophil responders. Proportion of responders and the associated 95% confidence interval will be presented for each treatment group. The between group difference and the associated 95% confidence interval will also be computed and presented. A sample SAS code is as follows.

```
* COMPUTE 95% EXACT CONFIDENCE INTERVAL FOR %RESPONSE FOR INDIVIDUAL
TREATMENT ;
ods output BinomialCLs=CL ;
proc freq data=ADEF ;
    table RESP / out=CNFS bin(cl=midp) ;
    by TRTAN ;
run;

* COMPUTE 95% EXACT CONFIDENCE INTERVAL AND FISHERS EXACT P-VALUE FOR
BETWEEN TREATMENT DIFFERENCE ;
ods output FishersExact=PVAL(where=(name1='XP2_FISH'))
RiskDiffCol2=DIFF(where=(row='Difference')) ;
proc freq data=ADEF ;
    table TRTPN*RESP / riskdiff(cl=exact) exact ;
run ;
```

### 6.11.2 Sensitivity Analysis of the First Co-Primary Endpoint

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

A sample SAS code for the pairwise comparison is as follows.

```
* COMPUTES CMH P-VALUE AND NEWCOMBE COMMON RISK DIFFERENCE ;
ods output CMH=PVAL (where=(althypothesis='Row Mean Scores Differ'))
CommonPdiff=DIFF;
proc freq data=ADEF ;
    tables TSS_STRAT*TRTP*RESP / cmh commonriskdiff
    (cl=NEWCOMBE) ;
run ;
```

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

### 6.11.3 Subgroup Analysis of the First Co-primary Endpoint

Analysis comparing AK002 and placebo will use the Fisher's exact test for each of the subgroups defined in Section 5.9.

### 6.11.4 Analysis of the Second Co-Primary Endpoint

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

The weekly TSS score is calculated as the average of the daily TSS scores. Weekly TSS will be set to missing if  $>3$  daily TSS are missing. Baseline TSS score will be the average of the last 2 weeks of daily TSS collected prior to the first infusion. The model variance-covariance matrix will be unstructured. However, if computation does not converge, the matrix will take the form of Toeplitz, autoregressive, or compound symmetry, whichever converges first. A sample of the SAS code for MMRM analysis is provided as below:

```

proc mixed data=tss method=reml;
  class TRTMT USUBJID AVISITN ANALYSIS_CENTER GENDER;
  model CHG= B_TSS TRTMT AVISITN ANALYSIS_CENTER GENDER
    TRTMT*AVISITN B_TTS*AVISITN / DDFM=KR;
  REPEATED AVISITN / SUBJECT=USUBJID (TRTMT) TYPE=UN;
  RANDOM ANALYSIS_CENTER;
  LSMEANS TRTMT*AVISITN / PDIF CL;
ESTIMATE 'PBO VS. AK002 at WEEKS 23-24' TRTMT -1 1
      TRTMT*AVISITN 0 0 0 0 0 0 0 0 0 0 0 -1
                  0 0 0 0 0 0 0 0 0 0 0 1 / CL;

RUN;

```

Where TRTMT = planned treatment group in numeric (1 = placebo, 2 = AK002); AVISITN = time point (i.e., Weeks 1-2, Weeks 3-4, ..., Weeks 23-24).

### 6.11.5 Sensitivity Analyses of the Second Co-Primary Endpoint

The two sensitivity analyses planned below are constructed based on the already imputed biweekly data set from Section 5.4.2.

The first sensitivity analysis is based on the placebo-based pattern-mixture model for the missing data imputation under the missing not at random (MNAR) assumption. In this model, subjects from the active treatment group after the ICE are assumed to behave like the subjects from the placebo group. Their missing data are imputed using the response profile from the placebo subjects who have similar baseline covariates and prior response trajectory. The sample SAS code follows.

/\*Step 1: Achieve Monotone Missing Data Pattern \*/

```

proc mi data=tss seed=135791 nimpute=50 out=mono;
  var B_EOS B_TSS TSS_W01_02 TSS_W03_04 ... TSS_W21_22
      TSS_W23_24;
  MCMC impute=monotone nbiter=200 niter=100;
  By TRTMT;
run ;

```

/\*Step 2: Achieve Control-Based Copy-Reference Imputation \*/

```

proc mi data=mono seed=135791 nimpute=50 out=outm1;
  class TRTMT;
  by _imputation_;
  var TRTMT B_EOS B_TSS TSS_W01_02 TSS_W03_04 ... TSS_W21_22
      TSS_W23_24;

```



```

        monotone reg;
        mnar model (TSS_W01_02 TSS_W03_04 ... TSS_W21_22 TSS_W23_24 /
            modelobs=(TRTMT='0')); * CODE 0 IS FOR PLACEBO GROUP ;
run ;

/*Step 3: Run MMRM Analysis on Imputed Data */

proc mixed data=tss method=reml;
    class TRTMT USUBJID AVISITN ANALYSIS_CENTER GENDER;
    model CHG= B_TSS TRTMT AVISITN ANALYSIS_CENTER GENDER
    TRTMT*AVISITN B_TTS*AVISITN / DDFM=KR;
    REPEATED AVISITN / SUBJECT=USUBJID (TRTMT) TYPE=UN;
    RANDOM ANALYSIS_CENTER;
    LSMEANS TRTMT*AVISITN / PDIF CL;
        ESTIMATE 'PBO VS. AK002 at WEEKS 23-24' TRTMT -1 1
            TRTMT*AVISITN 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 1 / CL;

    ODS OUTPUT PARAMETERESTIMATES=PESTIMATES;
run;

/*Step 4: Combining estimates from each imputed data set */

proc mianalyze data=PESTIMATES;
    modeleffects ESTIMATE;
    stderr stderr;
    by label;
    ods output PARAMETERESTIMATES=miparm;
run ;

```

The second sensitivity analysis is based on ANCOVA using the imputed data set (Section 5.4.2). The LS mean, SE, and 95% CI for each treatment group and for the between group difference will be derived from ANCOVA with treatment as factor, baseline PRO TSS (continuous) as covariates. The hypothesis test for the treatment effect will be carried out by the F-test. The synthesizing method will be used to combine the results from multiple imputations. The sample SAS code follows.

```

/** ANCOVA by imputation */
ods output diffs=diffs lsmeans=ls;
proc mixed data=ADIMP1 method=reml;
    where PARAMCD='TSS6' and ATPT='Weeks 23-24';
    by IMPUTED1;
    class gender analysis_center TRT01P;
    model CHG=gender analysis_center BASE TRT01P;
    lsmeans TRT01P / diff;
quit;
ods output close;

```

```
/** Combine LS Means (by treatment and difference) */  
data lsmdiff;  
    set lsm diffs(in=d);  
    if d then trt01p='DIFF';  
run;  
  
proc sort;  
    by trt01p;  
run;  
  
/** Synthesized results */  
ods output ParameterEstimates=SYNDIF;  
proc mianalyze data=LSMDIFF alpha=0.05;  
    by trt01p;  
    modeleffects ESTIMATE;  
    stderr STDERR;  
run;  
  
ods output close;
```

### 6.11.6 Supplementary Analyses

Analysis of Section 6.11.2 will be repeated for the Per Protocol population.

Additional analysis will investigate the treatment effect on PRO TSS change from baseline in the subgroups defined in Section 5.9. This analysis will use MMRM similarly to the primary analysis (Section 6.11.2).

Empirical cumulative distribution function (eCDF) of the change from baseline in TSS will be plotted by treatment group to demonstrate consistency of the treatment effect.

## 6.12 Analysis of Secondary Efficacy Endpoints

### 6.12.1 Change in Tissue Eosinophil Count

For subjects who provide duodenal biopsy, the calculation will be based on the average count of the highest readings from the respective mucosa at baseline and Day 169 (Week 24). The change in tissue eosinophil count from baseline to Day 169 will be analyzed using ANCOVA with treatment as factor, baseline eosinophil counts, baseline PRO TSS as covariates. The LSM, SE, and 95% CI for individual treatment groups, and LSM, SE, 95% CI, and p-value for the between treatment difference will be presented.

### 6.12.2 Proportion of Subjects Achieving Peak Duodenal Intraepithelial Eosinophil Count of $\leq 1$ Cell/hpf

This endpoint will be analyzed using the Fisher's exact test similar to the analysis for the first co-primary endpoint (Section 6.11.1).

### 6.12.3 Proportion of Treatment Responders

Treatment responder is defined as >30% improvement in TSS and mean eosinophil count  $\leq 15$  cells/hpf in 3 highest duodenal hpf. This endpoint will be analyzed using Fisher's exact test similar to Section 6.11.1.

### 6.12.4 Proportion of Subjects with $\geq 50\%$ Reduction and $\geq 70\%$ Reduction in TSS from Baseline to Weeks 23–24

These 2 endpoints will be analyzed using the CMH test stratified by the randomization stratification factor.

### 6.12.5 Change in Weekly TSS Over Time

Prior to the analysis, the missing weekly TSS scores will be imputed similarly to the imputation for the missing biweekly PRO TSS scores (Section 5.4.2). The imputed data sets will be analyzed using the mixed model for repeat measures (MMRM) similar to the analysis for the second co-primary endpoint.

The rationale for using the MMRM model is that this analysis is appropriate assuming subjects with missing data behave similarly to other subjects in the same treatment group. Having included in the model baseline symptom score (TSS), and response trajectory prior to missing, it is reasonable to believe that the missing data are either completely at random (MCAR) or at random (MAR) in this setting. In another words, if missing mechanism is not MCAR, it is likely explainable by the above model covariates and response trajectory.

## 6.13 Analysis of Exploratory Endpoints

### 6.13.1 Change in

Change from baseline in the number of in CCI will be analyzed using

### 6.13.2 Change in

Change from baseline in summary (including domain scores) will be analyzed using

similar to Section 6.12.5.

### 6.13.3 Change in

Change from baseline in will be analyzed using

#### 6.13.4 Change in [REDACTED]

Changes in [REDACTED] from baseline compared to post-treatment in the [REDACTED] [REDACTED] will be analyzed using [REDACTED]

#### 6.13.5 [REDACTED]

Change from baseline in [REDACTED]

will be analyzed using the [REDACTED] similar to the [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED] the analysis variable, will be based on the [REDACTED]

and calculated as the [REDACTED]

to establish a [REDACTED]

The data will be analyzed by [REDACTED] at Weeks 23-24. The sample SAS code follows.

[REDACTED]

[REDACTED]

- [REDACTED], the analysis variable, will be the [REDACTED] (defined as [REDACTED] and calculated as the [REDACTED] [REDACTED] to establish a [REDACTED] Analyzed in a [REDACTED]

### 6.13.6 CCI and CCI

Methods for CCI and CCI are described in a separate analysis plan.

## 6.14 Analysis of Pharmacokinetic Endpoint

The analysis of the PK concentration will be based on the Safety population. AK002 concentrations will be listed by treatment, subject, nominal time, and actual time. Concentrations that are below limit of quantification (BLOQ) will be indicated in the listing.

Plasma concentrations will be summarized at each nominal time point separately for each treatment. The following descriptive statistics will be presented: n, arithmetic mean, SD, geometric mean, % CV, median, minimum, and maximum.

Individual plasma concentration vs. actual times will be plotted for each subject in linear and semi-logarithmic scales, placed on the same page. Mean plasma concentration at the scheduled time points will be plotted for each treatment in linear and semi-logarithmic scale, with the associated standard errors (for linear scale only) at each scheduled time point.

In the plot, concentrations that are BLOQ will be assigned a value of 0 if they are collected predose or assigned a value of 1/2 the lower limit of quantification (LLOQ) if they are collected postdose.

Analysis of PK parameters are specified separately in a PK analysis plan.

## 6.15 Safety Analyses

### 6.15.1 Adverse Events

Safety assessments will be based mainly on the nature, frequency, relationship, and severity of adverse events (AE). The AE will be coded by primary System Organ Class (SOC) and Preferred Term (PT) according to MedDRA (version 21.0). The treatment-emergent adverse events (TEAE) 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 AE are reported with the same PT, the AE of the strongest relation to study drug will be included in the 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 TEAE to include
  - Number (%) of subjects who reported at least 1 TEAE
  - Number (%) of subjects who reported at least 1 treatment-related TEAE
  - Number (%) of subjects who reported at least 1 severe TEAE
  - Number (%) of subjects who reported at least 1 serious TEAE
  - Number (%) of subjects who reported at least 1 TEAE leading to treatment discontinuation
  - Number (%) of subjects who reported at least 1 TEAE leading to study discontinuation
  - Number (%) of subjects who reported at least 1 TEAE of special interest (TEAESI)
- TEAE by PT sorted by decreasing order of subject incidence in the combined treatment group
- TEAE by SOC and PT in alphabetical order
- TEAE by SOC, PT, and maximum severity
- TEAE by SOC, PT, and strongest relationship to study drug
- TEAE leading to treatment discontinuation by SOC and PT, if warranted by sample size
- TEAE leading to study discontinuation by SOC and PT, if warranted by sample size
- Serious TEAE by SOC and PT, if warranted by sample size
- TEAESI by SOC and PT

All AE 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 TEAE leading to study discontinuation, TEAE of special interest, and treatment-emergent serious AE (TESAE).

### **6.15.2 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 at each visit.

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

Note that the analysis window will be applied for the visits.

A complete laboratory data listing, including hematology, biochemistry, and urinalysis will be provided for all subjects.

### **6.15.3 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 visit (per analysis window) and time point. A data listing will include vital signs from all visits.

### **6.15.4 Electrocardiogram**

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

### **6.15.5 Physical Examination**

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

### **6.15.6 Analysis of Anti-Drug Antibody**

A data listing of anti-drug-antibodies (ADA) results will be provided for all subjects. Number (%) of subjects who are confirmed ADA-positive at any time after receiving study drug and number (%) of subjects who are confirmed ADA-positive at the end of study will be cross-tabulated by their ADA status and titers at predose.

## **7. Validation**

The Clinical Operations and Data Management at Allakos will work with the 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 eCRF 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 (TLF) based on the clinical data is outsourced. Allakos seeks to ensure the quality of the reports provided by the CRO in the form of TLF 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 TLF will be checked for completeness and consistency prior to delivery to Allakos.

## 8. References

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

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



## **9. Appendices**

- 9.1 [Appendix 1: Effect of Missing Data on the Weekly Mean of TSS](#)
- 9.2 [Appendix 2: Intercurrent Events](#)
- 9.3 [Appendix 3: List of Tables, Figures, and Listings](#)
- 9.4 [Appendix 4: Example SAS Codes](#)

## 9.1 Appendix 1: Effect of Missing Data on the Weekly Mean of TSS

Following the FDA's suggestion for the evaluation of the missing daily diary effect on the weekly mean of TSS score, data from the Phase 2 study are extracted. The Phase 2 study has diaries collected daily over 14 weeks of the treatment period. A simulation study was conducted examining the changes in standard error by the number of missing daily diaries that were randomly created. The step are as follows.

- 1) A complete date set is created in which a subject week is kept only if the week has all 7 daily diaries. This data set is at the subject-day level.
- 2) For each week in the complete data set, 1 of the 7 daily diaries is randomly set to missing. This creates a data set with 1 day per week missing.
- 3) Step 2 is repeated for 2 of the 7 daily diaries are randomly set to missing to create a data set with 2 day per week missing.

Finally, a data set is created with 6 days per week are randomly set to missing.

- 4) For each of the 7 data sets (0 day/week missing, 1 day/week missing, ..., 6 days/week missing), daily diaries are averaged to derive the weekly mean for each subject at each week.
- 5) Weekly means of the diaries are further averaged across all subjects to derive the population means and population standard error of the diaries for each week.
- 6) Steps 2 through 5 are repeated 500 times. Each time, the daily diaries are randomly set to missing.
- 7) The 500 weekly population standard errors from Step 6 are averaged and presented in the table below.

As expected, the standard error increases as the number of missing daily diaries increases, indicating the estimate of weekly TSS mean becomes less accurate. However, the increase in the standard error does not exceed 2% when allowing 3 out of 7 daily diaries missing, and does not exceed 4% when allowing 4 out of 7 daily diaries missing.

**Table 7**      **Standard Errors for the Mean Weekly TSS Diaries by Number of Daily Diaries Missing Averaged over 500 Simulations**

Week	Number of Daily Diaries Missing						
	0 Day	1 Day	2 Days	3 Days	4 Days	5 Days	6 Days
1	3.092	3.100	3.115	3.132	3.166	3.232	3.405
2	2.917	2.923	2.929	2.941	2.964	3.003	3.102
3	3.070	3.081	3.088	3.095	3.125	3.198	3.321
4	2.862	2.868	2.874	2.881	2.894	2.926	2.994
5	3.111	3.118	3.122	3.134	3.149	3.187	3.293
6	3.135	3.137	3.147	3.154	3.170	3.191	3.279
7	3.039	3.045	3.054	3.067	3.093	3.140	3.283
8	3.842	3.846	3.849	3.858	3.871	3.884	3.959
9	2.854	2.869	2.874	2.899	2.932	3.021	3.176
10	2.823	2.829	2.840	2.845	2.857	2.886	3.010
11	2.997	3.002	3.010	3.008	3.037	3.069	3.148
12	2.656	2.661	2.671	2.689	2.691	2.731	2.842
13	2.864	2.879	2.886	2.905	2.950	3.011	3.208
14	2.388	2.402	2.414	2.437	2.474	2.580	2.795

Source: K:\AK002-016\planning\MissingOnSE.sas 08MAR2020

## 9.2 Appendix 2: Intercurrent Events

- A. Use of any of the following prohibited medications during the course of the study as described
- 1) Immunosuppressive or immunomodulatory drugs (e.g., IL-5 modulators, i.e., benralizumab, reslizumab, mepolizumab; IL-4 and IL-13 antagonists, i.e., dupilumab; calcineurin inhibitors, i.e., cyclosporin, tacrolimus; mTOR inhibitors, i.e., sirolimus, everolimus; anti-metabolites, i.e., azathioprine, methotrexate, 6-mercaptopurine, leflunomide, mycophenolate mofetil; alkylating agents, i.e., cyclophosphamide; TNF inhibitors, i.e., infliximab, adalimumab; anti-IgE antibodies, i.e., omalizumab; and eosinophil-depleting drugs, i.e., pramipexole.
    - a) Use at any point during the study.
  - 2) Glucocorticoids
    - a) Initiation of any course of treatment or single use of systemic or swallowed corticosteroids at a dose of >10 mg/day prednisone or equivalent starting at Week 21 and through the end of Week 24. This does not include use of corticosteroids given as pre-infusion prophylaxis or treatment of IRR.
- B. Use of restricted medications outside the protocol-defined specifications
- 1) Glucocorticoids
    - a) Discontinuation of a previously stable dose of systemic or swallowed corticosteroids ( $\leq 10$  mg/day prednisone or equivalent) after the screening period.
    - b) Initiation of a new course of systemic or swallowed corticosteroids ( $\leq 10$  mg/day prednisone or equivalent) following the screening period and continuing to at least study Week 21 (within 2 weeks of efficacy assessment at Weeks 23 and 24).
  - 2) Proton Pump Inhibitors
    - a) Discontinuation of a previously stable dose of an oral PPI after the screening period and before the end of Week 24.
    - b) Initiation or increase in the dose of an oral PPI following the screening period and continuing to at least study Week 21 (within 2 weeks of efficacy assessment at Weeks 23 and 24).
  - 3) Sodium cromolyn
    - a) Discontinuation of a previously stable dose of sodium cromolyn after the screening period and before the end of Week 24

- b) Initiation or increase in the dose of sodium cromolyn following the screening period and continuing to at least study Week 22 (within 1 week of efficacy assessment at Weeks 23 and 24).

### C. Discontinuation of Investigational Medical Product

- 1) Discontinuation of study agent due to:
  - a) Infusion-related reaction
  - b) Subject withdrawal
  - c) Meeting study withdrawal criteria (Protocol Section 13.10)

Per protocol, subjects are required to remain on stable doses of either PPI or corticosteroids ( $\leq 10$  mg prednisone equivalent per day) throughout the course of the study if they are on a stable dose during the screening period. Because of the potential impact of corticosteroids and PPI on both histologic assessment of tissue eosinophil levels as well as subject reported GI symptoms, subjects must meet the entry requirements for both histology and symptom burden (TSS6) if they are on any of these medications at screening and therefore must remain on a stable dose throughout the study in order to meaningfully interpret any change from baseline during the evaluation phase. Conversely, subjects starting these medications due to unforeseen medical necessity following the screening period and remaining on them through a time point sufficiently close to the evaluation period to potentially impact assessment of symptoms and/or histologic assessments will be considered as intercurrent events. For PPI and corticosteroids ( $\leq 10$  mg/day prednisone or equivalent) a conservative washout period is estimated at 2 weeks, and therefore, continuation of a new course of therapy beyond Week 21 could be considered as a potential ICE.

Sodium cromolyn is a mast cell stabilizer and could potentially impact reported symptoms in a similar way to 1 of the mechanisms of action of AK002. As such, discontinuation of a previously stable dose of sodium cromolyn after the screening period and before the end of Week 24 could be considered as a potential ICE. Likewise, the initiation or increase in the dose of sodium cromolyn following the screening period and continuing to at least study Week 22 (within 1 week of efficacy assessment at Weeks 23 and 24) could be considered as a potential ICE. It is estimated that 1 week would be a sufficient washout period for the effects of sodium cromolyn.

Antihistamines are unlikely to impact histologic assessments in the study but could have slight impact in some symptoms depending on the type, dose, and duration of use. As such, subjects are required to stay on stable doses of antihistamines if they are taking them at the time of screening and to remain on them through completion of the study. Due to unforeseen medical circumstances and acknowledging that some subjects may have concurrent allergic conditions, the use of these medications by some subjects during the study is anticipated.

### 9.3 Appendix 3: List of Tables, Figures, and Listings

#### Tables

Table 14.1.1a	Subject Disposition and Reason for Discontinuation (All Screened Subjects)
Table 14.1.1b	Subject Disposition and Reason for Discontinuation (Safety/MITT Population)
Table 14.1.1c	Subject Disposition and Reason for Discontinuation (Evaluable Population)
Table 14.1.1d	Subject Disposition and Reason for Discontinuation (Excluded Population)
Table 14.1.1e	Subject Disposition and Reason for Discontinuation (Per Protocol Population)
Table 14.1.2	Major Protocol Deviations During the Study: Subject Count (All Randomized Subjects)
Table 14.1.3	Analysis Population: Subject Count (All Randomized Subjects)
Table 14.1.4	Per Protocol Population Exclusion (All Randomized Subjects)
Table 14.1.5a	Demographics and Baseline Characteristics (Safety/MITT Population)
Table 14.1.5b	Demographics and Baseline Characteristics (Evaluable Population)
Table 14.1.5c	Demographics and Baseline Characteristics (Excluded Population)
Table 14.1.5d	Demographics and Baseline Characteristics (Per Protocol Population)
Table 14.1.6a	Medical History by System Organ Class and Preferred Term: Subject Incidence (Safety/MITT Population)
Table 14.1.6b	Medical History by System Organ Class and Preferred Term: Subject Incidence (Evaluable Population)
Table 14.1.7.1	Study Drug Exposure (Safety Population)
Table 14.1.7.2	Study Drug Exposure (Safety Population)
Table 14.1.7.3	Duration of Treatment Exposure and Compliance (Safety Population)
Table 14.1.8.1a	Prior Medications by Anatomic Therapeutic Chemical Classification and Preferred Term: Subject Incidence (Safety Population)

Table 14.1.8.1b	Prior Medications by Anatomic Therapeutic Chemical Classification and Preferred Term: Subject Incidence (Evaluable Population)
Table 14.1.8.2	Concomitant Medications by Anatomic Therapeutic Chemical Classification and Preferred Term: Subject Incidence (Safety Population)
Table 14.1.9	Severity of Concomitant Asthma and Atopic Dermatitis at Baseline (MITT Population)
Table 14.1.10	12-Lead ECG Evaluation at Baseline (Safety Population)
Table 14.1.11a	Baseline Eosinophil and CCI Counts (MITT Population)
Table 14.1.11b	Baseline Eosinophil and CCI Counts (Evaluable Population)
Table 14.1.12a	Baseline Dysphagia Severity Score (MITT Population)
Table 14.1.12b	Baseline Dysphagia Severity Score (Evaluable Population)
Table 14.1.13a	Baseline Subject Reported Outcome Total and Symptom Scores (MITT Population)
Table 14.1.13b	Baseline Subject Reported Outcome Total and Symptom Scores (Evaluable Population)
Table 14.1.14	Baseline Vital Signs (MITT Population)
Table 14.1.15a	Subject Incidence of Intercurrent Events (MITT Population)
Table 14.1.15b	Subject Incidence of Intercurrent Events (Evaluable Population)
Table 14.2.1.1a	Tissue Eosinophil Responder at Week 24 – Primary and Sensitivity Analysis (Evaluable Population)
Table 14.2.1.1b	Tissue Eosinophil Responder at Week 24 – MITT Population
Table 14.2.1.1c	Tissue Eosinophil Responder at Week 24 – Excluded Population
Table 14.2.1.2.1	Tissue Eosinophil Responder at Week 24 by Gender (Evaluable Population)
Table 14.2.1.2.2	Tissue Eosinophil Responder at Week 24 by Age Group (Evaluable Population)
Table 14.2.1.2.3a	Tissue Eosinophil Responder at Week 24 by Baseline Peripheral Eosinophil Count Subgroup (Evaluable Population)

Table 14.2.1.2.3b	Tissue Eosinophil Responder at Week 24 by Race (Evaluable Population)
Table 14.2.1.2.3c	Tissue Eosinophil Responder at Week 24 by IgE Group (Evaluable Population)
Table 14.2.2.1a	Change from Baseline in Average of Weeks 23-24 PRO Total Symptom Scores – Primary Analysis – MMRM (Evaluable Population)
Table 14.2.2.1a	Change from Baseline in Average of Weeks 23-24 PRO Total Symptom Scores – MMRM (MITT Population)
Table 14.2.2.1c	Change from Baseline in Average of Weeks 23-24 PRO Total Symptom Scores – MMRM (Excluded Population)
Table 14.2.2.2	Change from Baseline in Average of Weeks 23-24 PRO Total Symptom Scores – Sensitivity Analysis 1 – Weekly TSS Due to ICE are Replaced/Imputed Using Placebo-Based Pattern-Mixture Model Multiple Imputation (Evaluable Population)
Table 14.2.2.3	Change from Baseline in Average of Weeks 23-24 PRO Total Symptom Scores – Sensitivity Analysis 2 – Weekly TSS Due to ICE are Replaced/Imputed Using Multiple Imputation by the MCMC Method (Evaluable Population)
Table 14.2.2.4	Change from Baseline in Average of Weeks 23-24 PRO Total Symptom Scores – MMRM (Per Protocol Population)
Table 14.2.2.5.1	Change from Baseline in Average of Weeks 23-24 PRO Total Symptom Scores by Gender – MMRM (Evaluable Population)
Table 14.2.2.5.2	Change from Baseline in Average of Weeks 23-24 PRO Total Symptom Scores by Age Group – MMRM (Evaluable Population)
Table 14.2.2.5.3a	Change from Baseline in Average of Weeks 23-24 PRO Total Symptom Scores by Baseline Peripheral Eosinophil Count Subgroup – MMRM (Evaluable Population)
Table 14.2.2.5.3b	Change from Baseline in Average of Weeks 23-24 PRO Total Symptom Scores by Race – MMRM (Evaluable Population)
Table 14.2.2.5.3c	Change from Baseline in Average of Weeks 23-24 PRO Total Symptom Scores by Baseline IgE Group – MMRM (Evaluable Population)



Table 14.2.3	Change from Baseline to Week 24 Tissue Eosinophil Count (Evaluable Population)
Table 14.2.4	Subjects Achieving Duodenal Intraepithelial Eosinophils Count $\leq 1$ cell/hpf (Evaluable Population)
Table 14.2.5	Subjects Achieving Tissue Eosinophil and TSS Treatment Response (Evaluable Population)
Table 14.2.6	Subjects with $\geq 50\%$ Reduction and $\geq 70\%$ Reduction in TSS from Baseline to Weeks 23-24 (Evaluable Population)
Table 14.2.7	Change from Baseline in Weekly TSS from Week 1 Through Week 24 Using MMRM (Evaluable Population)
Table 14.2.8	Change from Baseline to Week 24 [REDACTED] (Evaluable Population)
Table 14.2.9.1	Change from Baseline in [REDACTED] – Physical Component Summary (Evaluable Population)
Table 14.2.9.2	Change from Baseline in [REDACTED] – Mental Component Summary (Evaluable Population)
Table 14.2.10	Change from Baseline in [REDACTED] (Evaluable Population)
Table 14.2.11.1	Change from Baseline in Weekly [REDACTED] (Evaluable Population)
Table 14.2.11.2	Change from Baseline in Weekly [REDACTED] (Evaluable Population)
Table 14.2.11.3a	Change from Baseline in Weekly [REDACTED] (Evaluable Population)
Table 14.2.11.3b	Change from Baseline in Weekly [REDACTED] (Evaluable Population)
Table 14.2.11.4a	Change from Baseline in Weekly [REDACTED] (Evaluable Population)
Table 14.2.11.4b	Change from Baseline in Weekly [REDACTED] (Evaluable Population)

Table 14.2.11.5	Change from Baseline in Weekly (Evaluable Population)	CCI
Table 14.2.11.6	Change from Baseline in Weekly (Evaluable Population)	CCI
Table 14.2.11.7	Change from Baseline in Weekly (Evaluable Population)	CCI
Table 14.2.11.8	Change from Baseline in Weekly (Evaluable Population)	CCI
Table 14.2.12	Severity of Dysphagia at Baseline and Post-Baseline (Evaluable Population)	
Table 14.2.13	Morphological Assessment of Gastric Biopsies by Sydney System (Evaluable Population)	
Table 14.2.14	Morphological Assessment of Duodenal Biopsies by Marsh Scale Classification (Evaluable Population)	
Table 14.2.15	Change from Baseline in Body Weight (Evaluable Population)	
Table 14.2.16	Total Serum IgE Concentration (Evaluable Population)	
Table 14.2.17a	Subject Incidence of Positive Anti-Drug (AK002) Antibody (ADA) Test (Safety Population)	
Table 14.2.17b	Subject Incidence of Positive Anti-Drug (AK002) Antibody (ADA) Test (Evaluable Population)	
Table 14.3.1.1a	Overview of Treatment-Emergent Adverse Events (Safety Population)	
Table 14.3.1.1b	Overview of Treatment-Emergent Adverse Events (Evaluable Population)	
Table 14.3.1.2a	Treatment-Emergent Adverse Events by Preferred Term: Subject Incidence (Safety Population)	
Table 14.3.1.2b	Treatment-Emergent Adverse Events by Preferred Term: Subject Incidence (Evaluable Population)	
Table 14.3.1.3a	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term: Subject Incidence (Safety Population)	


Table 14.3.1.3b	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term: Subject Incidence (Evaluable Population)
Table 14.3.1.4a	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity: Subject Incidence (Safety Population)
Table 14.3.1.4b	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity: Subject Incidence (Evaluable Population)
Table 14.3.1.5a	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug: Subject Incidence (Safety Population)
Table 14.3.1.5b	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug: Subject Incidence (Evaluable Population)
Table 14.3.1.6a	Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term: Subject Incidence (Safety Population)
Table 14.3.1.6b	Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term: Subject Incidence (Evaluable Population)
Table 14.3.1.7a	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term: Subject Incidence (Safety Population)
Table 14.3.1.7b	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term: Subject Incidence (Evaluable Population)
Table 14.3.1.8a	Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term: Subject Incidence (Safety Population)
Table 14.3.1.8b	Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term: Subject Incidence (Evaluable Population)
Table 14.3.2.1	Hematology: Change from Baseline by Visit (Safety Population)
Table 14.3.2.2	Blood Chemistry: Change from Baseline by Visit (Safety Population)
Table 14.3.2.3	Hematology: Shift from Baseline Classification by Visit (Safety Population)

Table 14.3.2.4	Blood Chemistry: Shift from Baseline Classification by Visit (Safety Population)
Table 14.3.2.5	Urinalysis: Change from Baseline by Visit (Safety Population)
Table 14.3.3	Summary of Vital Signs by Visit (Safety Population)

## Figures

Figure 1	Cumulative Distribution Function Plot of Change from Baseline in Average of Weeks 23-24 TSS (Evaluable Population)
Figure 2	P-value from Between-Treatment Comparison in Weeks 23-24 TSS – Tipping Point Analysis (Evaluable Population)

**Listings**

- Listing 16.1.7 Subject Randomization Schedule (Randomized Population)
- Listing 16.2.1.1 Subjects Disposition and Reason for Disposition (Randomized Population)
- Listing 16.2.1.2 Subjects Who had Major Protocol Deviations (Randomized Population)
- Listing 16.2.1.3 Subjects Inclusion and the Reason for Exclusion from Analysis Populations (Randomized Population)
- Listing 16.2.1.4.1 Demographic and Baseline Characteristics (Safety Population)
- Listing 16.2.1.4.2 Demographic and Baseline Characteristics – History of Disease (Safety Population)
- Listing 16.2.1.5 Medical History (Safety Population)
- Listing 16.2.1.6 Diet Assessment (Safety Population)
- Listing 16.2.1.7.1 Prior Medications (Safety Population)
- Listing 16.2.1.7.2 Concomitant Medications (Safety Population)
- Listing 16.2.1.8 Intercurrent Events (Safety Population)
- Listing 16.2.2.1.1 Esophago-Gastro-Duodenoscopy (EGD) Biopsy Finding (Safety Population)
- Listing 16.2.2.1.2 Duodenal biopsy assessments (Safety Population)
- Listing 16.2.2.1.3 Esophageal biopsy assessments (Safety Population)
- Listing 16.2.2.2a Eosinophilic Gastritis and Gastroenteritis Questionnaire – Question Text (Safety Population)
- Listing 16.2.2.2b Eosinophilic Gastritis and Gastroenteritis Questionnaire – Daily Score (Safety Population)
- Listing 16.2.2.2c Eosinophilic Gastritis and Gastroenteritis Questionnaire – Weekly Score (Safety Population)
- Listing 16.2.2.3 Eosinophilic Gastritis Endoscopic Reference Score (EGERS) (Safety Population)
- Listing 16.2.2.4a  Questionnaire – Question Text

Listing 16.2.2.4b	CCI Questionnaire – Individual Questions (ITT Population)
Listing 16.2.2.4c	Questionnaire – Domain Scores (ITT Population)
Listing 16.2.2.5a	Intensity of Symptoms Questionnaire – Question Text (Safety Population)
Listing 16.2.2.5b	Intensity of Symptoms Questionnaire – Individual Scores (Safety Population)
Listing 16.2.3.1.1	All Adverse Events (Safety Population)
Listing 16.2.3.1.2	Serious Adverse Events (Safety Population)
Listing 16.2.3.1.3	Adverse Events with Outcome of Death (Safety Population)
Listing 16.2.3.1.4	Adverse Events Leading to Study Drug Discontinuation (Safety Population)
Listing 16.2.3.1.5	Adverse Events of Special Interest (Safety Population)
Listing 16.2.3.2.1	Clinical Laboratory Tests-Hematology (Safety Population)
Listing 16.2.3.2.2	Clinical Laboratory Tests – Blood Chemistry (Safety Population)
Listing 16.2.3.2.3	Clinical Laboratory Tests – Urinalysis (Safety Population)
Listing 16.2.3.2.4	Clinical Laboratory Tests – Diagnostic Immunology/Molecular Biology (Safety Population)
Listing 16.2.3.2.5	Clinical Laboratory Tests – Endocrinology (Safety Population)
Listing 16.2.3.2.6	Clinical Laboratory Tests – Parasitology (Safety Population)
Listing 16.2.3.2.7	Pre-Infusion Blood Collection (Safety Population)
Listing 16.2.3.3.1	Substance Use – Alcohol Consumption at Screening (Safety Population)
Listing 16.2.3.3.2	Urine Pregnancy Test (Safety Population)
Listing 16.2.3.4.1	Study Drug Administration (Safety Population)
Listing 16.2.3.4.2	Study Drug Accountability (Safety Population)
Listing 16.2.3.5	Vital Signs (Safety Population)
Listing 16.2.3.6	Subject Body Size (Safety Population)
Listing 16.2.3.7.1	12-Lead ECG Intervals at Baseline (Safety Population)

- Listing 16.2.3.7.2 12-Lead ECG Overall Interpretation (Safety Population)
- Listing 16.2.3.8 Physical Examination (Safety Population)
- Listing 16.2.3.9 Antidrug (AK002) Antibody (ADA) Test (Safety Population)
- Listing 16.2.3.10.1 Morphological Assessment of Gastric Biopsies by Sydney System (Safety Population)
- Listing 16.2.3.10.2 Morphological Assessment of Duodenal Biopsies by Marsh Scale Classification (Safety Population)
- Listing 16.2.3.10.3 Morphological Assessment of Esophageal Biopsy (Safety Population)
- Listing 16.2.3.11 Serum Concentrations of IgE (Safety Population)

## 9.4 Appendix 4: Example SAS Codes

```
/** Multiple Imputation **/  
proc mi data=TSS seed=1357986420 nimpute=50 out=TSS_IMPUTED1 ;  
    by TRTMT ;  
    mcmc chain=multiple impute=full initial=em nbiter=200 niter=100 ;  
var B_EOS B_TSS TSS_W01_02 TSS_W03_04... TSS_W21_22 TSS_W23_24 ;  
quit;  
/** Recalculate change from baseline **/  
data tss_imputed2;  
    set tss_imputed1;  
    chg=tss_w23_24 - b_tss;  
run;  
  
proc sort data=tss_imputed2 out=tss_imputed;  
    by _imputation_;  
run;  
  
/** ANCOVA by imputation **/  
ods output diffs=diffs lsmeans=ls;  
proc mixed data=tss_imputed method=reml;  
    by _imputation_;  
    class analysis_center gender TRTMT;  
    model CHG= analysis_center genderB_TSS TRTMT;  
    lsmeans TRTMT / diff;  
quit;  
ods output close;  
  
/** Combine LS Means (by treatment and difference) **/  
data lsmdiff;  
    set lsm diffs(in=d);  
    if d then trtmt='DIFF';  
run;  
  
proc sort;by TRTMT;run;  
  
/** Synthesized results **/  
ods output ParameterEstimates=SYNDIF;  
proc mianalyze data=LSMDIFF alpha=0.05;  
    by TRTMT;  
    modeleffects ESTIMATE;  
    stderr;  
run ;  
ods output close;
```