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

NCT Number: NCT04322708
Document Date: 10 Nov 2021

Statistical Analysis Plan for Protocol AK002-014

Protocol Title	A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AK002 in Adult and Adolescent Subjects with Active Eosinophilic Esophagitis
Protocol Number	AK002-014
Protocol Version	Amendment 6
Protocol Date	**Amendment 6 28 October 2021** Amendment 5 07 May 2021 Amendment 4 20 August 2020 Amendment 3 08 July 2020 Amendment 2 07 May 2020 Amendment 1 13 January 2020 Original 16 October 2019
Study Drug	AK002
Study Phase	2/3
IND Number	143997
Sponsor	Allakos Inc., 975 Island Drive, Suite 201, Redwood City, CA 94065 USA
SAP Version	1
SAP Date	**10 November 2021**

Signature Page

Prepared by:

PPD

10-Nov-2021 | 13:49 PST

PPD PhD
Director, Biometrics
Allakos Inc.

Date

Reviewed and Approved by:

PPD

10-Nov-2021 | 16:54 PST

PPD PhD
PPD Biometrics
Allakos Inc.

Date

PPD

11-Nov-2021 | 07:31 PST

PPD MD, MBA
PPD
Allakos Inc.

Date

Table of Contents

List of In-Text Tables

List of Abbreviations

ADA	Anti-drug antibody(ies)
ADaM	Analysis Data Model
AE	Adverse event(s)
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical Classification System
BLOQ	Below limit of quantitation
BMI	Body mass index
BZH	Basal zone hyperplasia
CBC	Complete blood count
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	Coefficient of variation
DEC	Dyskeratotic epithelial cells
DIS	Dilated intercellular spaces
DM	Data management
DSQ	Dysphagia Symptom Questionnaire
EA	Eosinophil abscess
ECG	Electrocardiogram
eCDF	empirical Cumulative Distribution Function
eCRF	electronic Case Report Form
EDC	Electronic Data Capture (system)
EG	Eosinophilic gastritis
EGD	Esophagogastroduodenoscopy
EI	Eosinophilic inflammation
EoE	Eosinophilic esophagitis
EoD	Eosinophilic duodenitis
CCI	[redacted]
EREFS	Eosinophilic Esophagitis Endoscopic Reference Score

ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GI	Gastrointestinal
hCG	human chorionic gonadotropin
hpf	High power field
ICE	Intercurrent event(s)
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IRR	Infusion-related reaction(s)
IRT	Interactive Response Technology
ITT	Intent-to-Treat (population)
IV	Intravenous
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LPF	Lamina propria fibrosis
LSM	Least squares mean(s)
MCMC	Markov Chain Monte Carlo (method)
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MITT	Modified Intent-to-Treat (population)
MMRM	Mixed Model for Repeated Measures
MNAR	Missing not at Random
OLE	Open-label extension (period)
CCI	[redacted]
CCI	[redacted]
PEC	Peak eosinophil count
PK	Pharmacokinetic(s)
PP	Per Protocol (population)
PPI	Proton pump inhibitor(s)
PT	Preferred term
PRO	Patient-reported outcome (questionnaire)
p-value	Probability value
SAE	Serious adverse event(s)

SAP	Statistical Analysis Plan
SEA	Surface epithelial alteration
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error(s)
CCI	[redacted]
SL	Surface layering
SOC	System organ class
TEAE	Treatment-emergent adverse event(s)
TEAESI	Treatment-emergent adverse event(s) of significant interest
TESAE	Treatment-emergent serious adverse event(s)
TLF	Tables, Listings, and Figures
TNF	Tumor necrosis factor
TSS	Total Symptom Score
ULN	Upper limit of normal
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

Revision History

Version Date	Version Number	Description
10 Nov 2021	1	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 adult and adolescent subjects with active eosinophilic esophagitis (EoE) 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 pharmacokinetics (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 AK002-014 Amendment 6, dated 28 October 2021, 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 adult and adolescent subjects when compared to placebo.

Efficacy endpoints will be co-primary:

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

2.2 Secondary Objectives – Secondary Endpoints

The secondary objectives are to evaluate the clinical benefit of AK002 in adult and adolescent subjects with active EoE when compared to placebo as measured by:

1) Percent change in peak esophageal intraepithelial eosinophil count at Week 24.
2) Proportion of subjects achieving peak esophageal intraepithelial eosinophil count of ≤1 eosinophil/hpf at Week 24.
3) Proportion of subjects achieving peak esophageal intraepithelial eosinophil count of <15 eosinophils/hpf at Week 24.
4) Proportion of treatment responders when a responder is a subject achieving >30% reduction in symptoms (DSQ) at Weeks 23–24 and achieving a peak intraepithelial eosinophilic count of ≤6 eosinophils/hpf at Week 24.

5) Proportion of subjects with >50% reduction in DSQ score from Baseline to Weeks 23–24.

6) Percent change in DSQ score from Baseline to Weeks 23–24.

7) Change in biweekly mean DSQ over time.

8) Change in EoE Endoscopic Reference Score (EREFS) from Baseline to Week 24.

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:

1) Change in components (Section 6.13.1) of CCI [redacted] from Baseline to Week 24.

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

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

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

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

Subjects will be consented and then screened for 14 to 60 days. During the screening period, a baseline, stable regimen of proton pump inhibitors (PPI) and/or dietary intake will be established, if needed, and baseline disease activity data will be collected. Swallowed topical corticosteroids and systemic corticosteroids will not be allowed. Subjects who meet eligibility criteria can be enrolled in the study. Subjects who do not meet all eligibility criteria at screening, or who qualify at screening but are not enrolled, may be assigned a new subject identification number and rescreened once. Subjects rescreened within 30 days of signing the initial informed consent form (ICF) will not need to reconsent if no changes have been made to the ICF.

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

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

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

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

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

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

The study design is summarized as follows:

- A 14 to 60-day (or a maximum of 35 days after the Screening esophagogastroduodenoscopy [EGD], whichever is shorter) Screening Period with baseline evaluations for eligibility, including baseline disease activity (by daily PRO questionnaire) and EGD with biopsy.
- Prior to the first dose of study drug (12–24 hours prior to the infusion), subjects will be premedicated with oral prednisone (40 mg if body weight is <40 kg, 60 mg if body weight is ≥40 kg and <60 kg, or 80 mg if body weight is ≥60 kg).
- Eligible subjects will receive 6 doses of AK002 (or placebo) by IV infusion on Days 1, 29 (±3), 57 (±3), 85 (±3), 113 (±3), and 141 (±3). Subjects will self-administer prednisone 12–24 hours prior to the start of the first infusion only.
- Subjects will remain at the site for at least 1 hour of observation after each dose. In the event of an IRR, the subject may require prolonged observation (>1 hour or until the symptoms resolve), as per Investigator discretion. Subjects will also be instructed to immediately contact the study doctor if any reactions occur after discharge.
- A repeat EGD with biopsy will be performed on Day 169 (±3) or 28 (±3) days after last dose if subject is terminated early between Day 29 and Day 169 study visits.

- After completion of the Day 169 visit, the Investigator will evaluate whether the subject is eligible for the OLE Period.
- Subjects who are eligible and choose to participate in the OLE Period will begin following the OLE Schedule of Events on Day 176 (±3). The OLE Period includes 6 doses of open-label AK002 administered on Days 176 (±3), 204 (±3), 232 (±3), 260 (±3), 288 (±3), and 316 (±3) and post-treatment follow-up visits on Day 344 (±7) and Day 372 (±7).
- Subjects who are not eligible for (or who choose not to participate in) the OLE Period will be followed for approximately 8 weeks after the last dose per the Schedule of Events (Table 1). The Follow-Up Period includes the Day 169 (±7) visit (4 weeks after the last dose) and the Day 197 (±7) visit (8 weeks after the last dose).
- If absolute lymphocyte and/or eosinophil counts have not recovered by the Day 197 visit (or the Day 372 visit for subjects participating in the OLE Period), subjects will return approximately every 28 days for extended follow-up until counts have recovered.
- Total study duration is approximately 33–36 weeks or 58–61 weeks for subjects participating in the OLE Period, though the study duration could be extended for monitoring absolute lymphocyte and/or eosinophil counts (as described above).

3.2 Schedule of Events

The schedule of procedures and assessments (excluding the OLE Period) is depicted in Table 1.

Table 1 AK002-014 Schedule of Events

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

Table 1 AK002-014 Schedule of Events cont.

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

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

Table 1 Notes

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

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

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

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

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

Table 1 Notes cont.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 1 Notes cont.

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

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

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

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

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

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

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

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

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

32) ET visits should be conducted 28 (±3) days after the last dose of study drug or prior to this, if necessary, to ensure compliance with the visit. If a subject discontinues the study >28 days after the last dose of study drug, the ET visit should be conducted as soon as possible. If the subject is terminated after Day 29 and before Day 169, the ET visit will be performed 28 (±3) days after last dose and the ET visit will follow the Day 169 assessment schedule (including EGD with biopsy collection). If the subject is not participating in the OLE period and the ET visit occurs after Day 169, the Day 197 assessment schedule should be followed for the ET visit. See Protocol Appendix 19.12 for the OLE Period Schedule of Events for OLE period ET after Day 176.

33) If absolute lymphocyte and/or eosinophil counts do not recover (to normal range or baseline levels) by Day 197 (or ET), extended follow-up visits are required every 28 (±3) days) to monitor blood counts until they recover. Extended follow-up visits consist of blood collection for CBC with differential and collection of AESI and SAE.

34) After completion of the Day 169 visit, the Investigator will evaluate whether the subject is eligible for the OLE period. If the subject is eligible, the subject will be given the option to participate in the OLE period beginning approximately 1 week after the Day 169 visit. Approximately 1 week after the Day 169 visit (on Day 176 ±3 days), eligible subjects that choose to participate in the OLE period will begin following the OLE Schedule of Events (Protocol Appendix 19.12) and will receive the first open-label AK002 infusion. For subjects participating in the OLE period, AE and concomitant medications should be collected and recorded in the AK002-014 Treatment Period database up until the start of the first open-label infusion during the Day 176 visit. This includes prednisone premedication administered prior to the Day 176 visit of the OLE period, which should be recorded in the Concomitant Medications CRF of both the AK002-014 treatment period database and the AK002-014 OLE period database.

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

3.3 Study Treatment

3.3.1 Treatment, Dose, and Mode of Administration

Subjects will be randomly assigned through the IRT system to receive 1 of 3 dose regimens in a double-blind fashion: placebo; the low dose regimen (1 mg/kg AK002 administered every 4 weeks for 6 doses); or the high dose regimen (1 mg/kg AK002 for the first dose followed by 3 mg/kg AK002 administered every 4 weeks for the 5 subsequent doses).

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

3.3.2 Duration of Study

The total study duration for each subject will be either 33–36 weeks or 58-61 weeks, including and depending on:

- Screening Period of 14–60 days (or a maximum of 35 days after the Screening EGD, whichever is shorter) prior to study drug administration.
- Treatment Period of 24 weeks (±3 days) beginning the day of the first dose and ending 4 weeks after the last dose
- Optional Open-Label Extended Dosing Period of 28 weeks (±3 days), or Follow-up period of 4 weeks (±3 days).

3.3.3 Methods of Assigning Subjects to Treatment Group

Approximately 300 subjects with active EoE will be randomized 1:1:1 to receive 1 of 3 dose regimens in a double-blind manner.

- AK002 at 1 mg/kg every 4 weeks for 6 doses
- AK002 at 1 mg/kg for the first dose, followed by 3 mg/kg administered every 4 weeks for 5 subsequent doses
- 6 doses of placebo

3.4 Blinding

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

3.5 Hypotheses

The hypothesis to be tested in the study is that AK002 is different from placebo with regards to the 2 co-primary efficacy endpoints of the proportion of subjects who achieve a peak esophageal intraepithelial count of ≤6 eosinophils/hpf at Week 24 and the mean reduction from baseline in DSQ score at Weeks 23–24.

3.6 Determination of Sample Size

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

To achieve statistical significance for the second co-primary endpoint, a sample size of 86 subjects per treatment group will provide 90% power to demonstrate a statistically significant difference between any AK002 dose group and placebo treatment group in mean absolute change in DSQ score from baseline to Weeks 23–24. This calculation is based on the baseline score of 30 ± 15 (mean ± Standard Deviation [SD]) reported in the literature, and an expected mean reduction of 15 in the AK002 group and 7.5 in the placebo group, and a SD of 15 for the change from baseline (Dellon, 2021; Hirano, 2019; Hudgens, 2017).

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

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 [redacted]) is defined as the non-missing value collected most recent to and before the time of the first dose of study drug. This includes lab tests collected on Day 1 Predose as an example. Baseline DSQ score is determined from 14 days prior to the first dose.
Completer for the Study	A subject who does not participate in the OLE period and who completes visits through the Day 197 visit or, if applicable, the last Extended Follow-Up visit after completing Day 197, will be recorded as having completed the double-blind portion of the study. A subject who completes visits through the Day 169 visit and participates in the OLE period of the study will be recorded as having completed the double-blind portion of the study. A subject who participates in the OLE period of the study and completes visits through the Day 372 visit or, if applicable, the last Extended Follow-Up visit after completing Day 372 will be recorded as having completed the OLE portion of the study.
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.
DSQ	Dysphagia Symptom Questionnaire: See Appendix 1 for the DSQ and the DSQ scoring algorithm.
EG/EoD Subject-Reported Outcome (PRO)	PRO questionnaire evaluates 8 different symptoms with 10 daily questions for intensity and frequency: • Abdominal pain intensity • Nausea intensity • Vomiting intensity • Vomiting frequency • Diarrhea intensity • Diarrhea frequency • Early satiety intensity • Loss of appetite intensity • Bloating intensity • Abdominal cramping intensity Each intensity evaluation is scored on a scale of 0=none to 10=worst possible.

Table 2 Terminology and Definitions cont.

Terminology	Definition
Enrolled	Subject who is randomized to a treatment group.
CCI [redacted]	[redacted]: See Appendix 1.
EREFS	EoE Endoscopic Reference Score: See Appendix 1.
Newly Initiated Medication	Refers to any medication with start date ≥ Study Day 1.
Prior Medication	Medication collected on the Prior/Concomitant Medication CRF with start date prior to Study Day 1.
PRO TSS	Total Symptom Score is the sum of 6 weekly average symptom intensity scores (abdominal pain, abdominal cramping, bloating, nausea, early satiety, and loss of appetite).
TEAE	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.
Tissue Eosinophil Responder	For subjects who achieve a peak esophageal intraepithelial count of ≤6 eosinophils/hpf at Week 24
Treatment Responder	Subjects who achieve a peak esophageal intraepithelial count of ≤6 eosinophils/hpf at Week 24 and achieve >30% reduction in biweekly DSQ score at Weeks 23–24.
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	Defined as 7 days a week starting from the day of first dose (Day 1).

4.2 Target of Estimation

The estimand (target of estimation) for Protocol AK002-014 is:

> *In subjects with active EoE, what is between group (AK002 vs. Placebo) difference in the proportion of tissue eosinophil responders at Week 24, and group difference in biweekly DSQ from baseline to Weeks 23–24 as measured by the patient reported Dysphagia Symptom 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 by the inclusion and exclusion criteria as part of the study protocol. Subjects must have a clinical diagnosis of active EoE.

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 DSQ from baseline to Weeks 23–24 as measured by the patient reported outcome (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/rescue medication
- Any therapeutic EGD (defined as dilatation or other intervention for a narrowing or stricture of the esophagus) at any point during the study through Week 24.

Further clarification and handling of ICE including prohibited/rescue medications is detailed in Appendix 2.

4.2.5 Strategy for Handling Intercurrent Events

Per the study protocol, if a prohibited medication is started during the course of the study, the subject will be withdrawn from study treatment and followed for the 12-week follow-up period. In addition, the follow-up EGD may not be performed. Thus, for analysis of the trial product estimand, tissue eosinophil values and DSQ scores will be counted as non-responders for binary variables and set to missing for continuous outcomes from the point when an ICE occurs. An appropriate method for handling missing data through statistical modeling (e.g., multiple imputation [MI]) will be used (Sections 5.4.1, 5.4.2, and 6.11). The estimand will provide an answer to the question that is crucial to individual subjects:

> "If I take this study drug as part of my treatment regimen, without adding any further medications or the use of therapeutic endoscopic interventions 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 Estimand

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

5. Statistical Methods

5.1 General Methodology

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

All CRF data (raw data) will be converted into SDTM (Study Data Tabulation Model) datasets, which will be used to create ADaM (Analysis Data Model) data sets. The creation of the SDTM and ADaM data sets will follow the CDISC (Clinical Data Interchange Standards Consortium) standards and the FDA Study Data 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, 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 each treatment group, the placebo, and the overall study population.

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 0.01×10^9/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 154
Day 169	Day 155 to Day 186
Day 197	Day 187 to End of Study

Table 4 Analysis Window Rules for Vital Sign and Laboratory Tests

Visit Description	Window
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 154
Day 169	Day 155 to 186
Day 197	Day 187 to End of Study

Table 5 Analysis Window Rules for PK Concentration and ADA

Visit Description	Window
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

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 15	Day 1 Postdose to Day 18
Day 29	Day 21 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 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, a 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 analysis of covariance (ANCOVA), mixed model for repeated measures (MMRM), or Cochran-Mantel-Haenszel (CMH) tests, where applicable.

5.4 Handling of Dropouts, Missing Data, and Data Discrepancies

5.4.1 Missing 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 post-baseline unscheduled visit prior to missing. If no eosinophil count is collected post-baseline, the subject will be considered treatment failure for tissue eosinophil response.

5.4.2 Missing Daily PRO Scores at Weeks 23–24

The PRO daily scores will be set to missing if they are collected after subjects have experienced an ICE. For the endpoint of change in the biweekly DSQ score, the biweekly average score will be calculated using the available daily scores. The validated DSQ calculation normalizes the missing daily scores within the 14-day, biweekly interval.

Missing DSQ scores during Weeks 23–24 will be imputed using the MCMC method. Baseline tissue eosinophil count and baseline DSQ and age strata will be included along with the average biweekly DSQ (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. Missing data imputation (PROC MI) will be conducted separately for active AK002 treatment groups. An example of the SAS code for this imputation follows.

```
proc mi data=DSQ seed=1357986420 nimpute=50
out=DSQ_IMMPUTED ;
      by TRTMT ;
      class AGE_STRATA;
      mcmc chain=multiple impute=full initial=em nbiter=200 niter=100 ;
var B_EOS B_DSQ DSQ_W01_02 DSQ_W03_04
... DSQ_W21_22 DSQ_W23_24 ;
run ;
```

After imputation, the LSM and 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=LSMDIFF alpha=0.05 ;
     by trtmt;
      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 Final Analyses

There will be 2 database locks for this study:

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

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

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

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

5.7 Multicenter Study

Supplemental analysis will be performed pooling data across study sites.

The study will have approximately 90 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 site effects. Sites from the following geographic clusters have been identified for pooling data across study sites:

- **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
- **Analysis Center 6:** ROW – sites in Australia and the Netherlands

5.8 Multiple Comparisons/Multiplicity Adjustment

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

Table 7 Hypothesis Testing Order Hierarchy

Endpoint Description	AK002 IV Dose Groups	
	Low Dose	High Dose
Primary Endpoints		
1) The proportion of subjects who achieve a peak esophageal intraepithelial count of ≤6 eosinophils/hpf at Week 24.	8	1
2) Mean change in DSQ score from Baseline to Weeks 23–24.		
Secondary Endpoints		
1) Percent change in peak esophageal intraepithelial eosinophil count at Week 24.	14	7
2) Proportion of subjects achieving peak esophageal intraepithelial eosinophil count of ≤1 eosinophil/hpf at Week 24.	9	2
3) Proportion of subjects achieving peak esophageal intraepithelial eosinophil count of <15 eosinophils/hpf at Week 24.	18	17
4) Proportion of treatment responders when a responder is a subject achieving >30% reduction in symptoms (DSQ) at Weeks 23–24 and achieving a peak intraepithelial eosinophilic count of ≤6 eosinophils/hpf at Week 24.	10	3
5) Proportion of subjects with >50% reduction in DSQ score from Baseline to Weeks 23–24.	12	5
6) Percent change in DSQ score from Baseline to Weeks 23–24.	11	4
7) Change in biweekly mean DSQ over time.	16	15
8) Change in EoE Endoscopic Reference Score from Baseline to Week 24.	13	6

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 (12–17, ≥18)
- Race (White, Non-White)
- Baseline DSQ (≤30, >30)

6. Statistical Analysis

6.1 Analysis Populations

The population of "all screened subjects" comprises subjects who signed the informed consent form (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 study drug.

6.1.4 Per Protocol Analysis population

The Per Protocol (PP) population will include the MITT population 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 MITT population is the primary analysis population for all efficacy and safety analyses. Analysis using the ITT population will be carried out if ≥5 randomized subjects do not receive study drug. The PP population will be used to evaluate robustness for the primary endpoints and select secondary endpoints when appropriate.

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 MITT and PP populations.

6.5 Baseline Disease Characteristics

Baseline disease characteristics including demographics, baseline DSQ score, and medical history 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 ICF 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 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 the last dose minus the date of the first dose, plus 1 (date of last dose – date of first dose +1).

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

Treatment compliance is defined as the number of infusions subjects received divided by 6 (i.e., total number of infusions expected) × 100%. Treatment compliance will be summarized descriptively. In addition, overall compliance that includes adherence to the 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 ≥ 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 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 PT 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 DSQ, and most recent tissue eosinophil count and 2-week average of DSQ).

A summary table will be created to present by treatment group number of subjects (n, %).

- 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% CI will be presented for each treatment group. The between group difference (pairwise comparison with placebo) and the associated 95% CI 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=CNTS 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 CMH test stratified by the randomization stratification factors (baseline DSQ and age) to assess robustness of 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 DSQ_Strata*AGE_STRAT*TRTP*RESP / cmh commonriskdiff
   (cl=NEWCOMBE) ;
run ;
```

The rationale for specifying Fisher's exact test as the primary analysis as opposed to specifying the CMH test 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 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 by ANCOVA (primary analysis) using the imputed data set (Section 5.4.2). The LSM, SE, and 95% CI for each treatment group and for the between group difference will be derived from ANCOVA with treatment as a factor, baseline DSQ and age 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.

6.11.5 Sensitivity Analyses of the Second Co-Primary Endpoint

The 2 sensitivity analyses planned below are constructed based on the already imputed bi-weekly data set from Section 5.4.2. From this imputed data set, the bi-weekly DSQ is set to missing if it is derived from the daily scores collected on/after ICE event. This setting creates the monotone missing data set.

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.

```
proc mi seed=135791 nimpute=10;
      class TRTMT;
         var B_EOS Age_Grp B_DSQ DSQ_W01_02 DSQ_W03_04 ... DSQ_W21_22
         DSQ_W23_24;
      monotone reg;
      mnar model(DSQ_W01_02 DSQ_W03_04 ... DSQ_W21_22 DSQ_W23_24 /
         modelobs=(TRTMT='0'));     * CODE 0 IS FOR PLACEBO GROUP ;
run ;
```

The second sensitivity analysis is based on the tipping point method. In this method, the missing biweekly DSQ will be imputed with different adjustments for the active treatment subjects and placebo subjects under the MNAR assumption in which the search for a tipping point reverses the study conclusion (i.e., p-value no longer <0.05 for the treatment effect). A shift ranging from -*x* to +*y* representing different level of improvement or worsening due to ICE will be added to the imputed DSQ. An example of the SAS code follows.

```
proc mi seed=579864 nimpute=10;
      class AGE_STRAT TRTMT;
      var B_EOS B_DSQ DSQ_W01_02 DSQ_W03_04 ... DSQ_W21_22 DSQ_W23_24;
      monotone reg;
      mnar  adjust(DSQ_W01_02 / adjustobs=(TRTMT='1') shift=&d1.)
            adjust(DSQ_W03_04 / adjustobs=(TRTMT='1') shift=&d1.)
            . . .
            adjust(DSQ_W21_22 / adjustobs=(TRTMT='1') shift=&d1.)
            adjust(DSQ_W23_24 / adjustobs=(TRTMT='1') shift=&d1.)
            adjust(DSQ_W01_02 / adjustobs=(TRTMT='0') shift=&d0.)
            adjust(DSQ_W03_04 / adjustobs=(TRTMT='0') shift=&d0.)
            . . .
            adjust(DSQ_W21_22 / adjustobs=(TRTMT='0') shift=&d0.)
            adjust(DSQ_W23_24 / adjustobs=(TRTMT='0') shift=&d0.);
run;
```

Note: A positive adjustment (shift>0) will increase (worsen) the DSQ score and a negative adjustment (shift<0) will reduce (improve) the DSQ score. Varying shift parameter from 0 (minimum) to maximum, where maximum shift parameter will be guided by the mean difference between subjects that drop out after the t^{th} visit and subjects that continue. This sensitivity analysis will vary the shift parameter independently between the active treatment subjects and placebo subjects.

After the data are imputed, the ANCOVA with the synthesizing method will be applied using methods described in Section 5.4.2.

P-values for the between treatment comparison from the synthesized ANCOVA results will be plotted against the shift parameters to demonstrate the robustness of the study conclusion against the various imputation strategies to account for the ICE effect.

6.11.6 Supplementary Analyses

Analysis described in Section 6.11.2 will be repeated for the PP population.

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

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

6.12 Analysis of Secondary Efficacy Endpoints

6.12.1 Percent Change in Tissue Eosinophil Count

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

6.12.2 Proportion of Subjects Achieving Peak Esophageal Intraepithelial Eosinophil Count of ≤1 and <15 Eosinophils/hpf at Week 24

These 2 endpoints will be analyzed using 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 DSQ at Weeks 23–24 and a peak esophageal intraepithelial eosinophil count ≤6 cells/hpf at Week 24. This endpoint will be analyzed using Fisher's exact test similar to Section 6.11.1.

6.12.4 Proportion of Subjects with >50% Improvement in DSQ from Baseline to Weeks 23–24

This endpoint will be analyzed using the CMH test stratified by the randomization stratification, age, and baseline DSQ factors.

6.12.5 Percent Change in DSQ from Baseline to Weeks 23–24

This endpoint will be analyzed using similar methods for the change in DSQ score as discussed in Section 6.11.4.

6.12.6 Change in Biweekly Mean DSQ Over Time

The data will be analyzed using the MMRM with age, treatment, week, and treatment-by-week interaction as fixed factors, baseline DSQ (continuous) as covariates, and subject as repeated measure unit over time. The model will use change from baseline in the biweekly DSQ from Weeks 1–2 through Week 23–24.

The model variance-covariance matrix will be unstructured. If the computation does not converge, the covariance matrix will take the form of Toeplitz, AR(1), and compound symmetry, whichever converges first. The improved Kenward-Rodger's method (SAS KR2 option) will be used to derive the denominator degrees-of-freedom. The LSM and 95% CI for the between group difference (active dose vs. placebo) will be estimated using the simple contrast at each week.

A sample SAS code is provided as follows.

```
proc mixed data=ADEF method=REML ;
   class TRTPN USUBJID WEEKS ;
   model CHG = B_DSQ AGE_STRAT TRTPN WEEKS TRTPN*WEEKS / ddfm=KR2 ;
   repeated WEEKS / subject=USUBJID(TRTPN) type=UN ;
   lsmeans TRTPN*WEEKS / pdiff cl ;
run ;
```

6.12.7 Change in EoE Endoscopic Reference Score

Change in EREFS from baseline to Week 24 will be analyzed using ANCOVA with age strata, treatment, and baseline EREFS.

The EREFS is the sum of 5 components with a maximum score of 9 for each location (proximal and distal esophagus) and maximum combined score of 18. Individual component score ranges are as follows:

- Edema 0–1
- Rings 0–3
- Exudates 0–2
- Furrows 0–2
- Stricture Range 0–1

Each component is scored based on the presence and/or grade of each feature. Miscellaneous features will not be included in the total score.

Improvements in inflammatory and remodeling features may also be reported based on individual scores for edema, rings, furrows, exudate, and stricture.

Inflammatory and fibrostenotic subscores will be generated (proximal, distal, and combined). The inflammatory subscore is the sum of the exudate, edema, and furrows scores (range 0–5). The fibrostenotic subscore is the sum of the rings and stricture scores (range 0–4).

6.13 Analysis of Exploratory Endpoints

Change in continuous exploratory endpoints collected at multiple post-baseline time points will be analyzed using MMRM and will include fixed effects for age, baseline value, treatment, visit, and the treatment-by-visit interaction and allow for random subject effects. Treatment and week will each be fitted as categorical variables. The model will assume unstructured covariance structure.

6.13.1 Change in CCI [redacted]

Change in the following components of the CCI [redacted] from baseline to Week 24 will be reported in a descriptive manner:

- CCI [redacted]

Change in the following components of the CCI [redacted] from baseline to Week 24 may be assessed post-database lock in addition to calculation of a total CCI [redacted] score:

- CCI [redacted]

6.13.2 Change in [CCI]

Change from baseline in [CCI] summary (including Domain) scores will be analyzed using [CCI] baseline [CCI] value as covariate, and subject as repeated measure unit over visits.

6.13.3 Change in [CCI]

Change from baseline in the number of [CCI] will be analyzed using [CCI] and baseline [CCI] as covariate.

6.13.4 [CCI]

Methods for [CCI] and [CCI] analysis 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 BLOQ (below limit of quantification) 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 SE (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 half the LLOQ (lower limit of quantification) 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 the AE, and AE will be coded by primary SOC and 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, TEAESI, and treatment-emergent SAE (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, SD, 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 visits will be classified into below (< LLN), within (≥ LLN and ≤ ULN), and above (> ULN) normal ranges. Subject incidences (n and %) will be presented for the shift from baseline to the post-baseline visits.

Note: 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, SD, ranges) for each visit (per analysis window) and time point. A data listing will include vital signs from all visits.

6.15.4 Electrocardiograms

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

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 electronic case report forms (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

Collins M, Martin L, Alexander E, Boyd J, Sheridan R, He H, et al. Newly developed and validated eosinophilic histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. Dis Esophagus, 2017;30:1–8.

Dellon E, Collins M, Katzka D, Hudgens S, Lan L, Williams J, et al. Improvements in dysphagia and pain with swallowing in patients with eosinophilic esophagitis receiving budesonide oral suspension. Clin Gastroenterol Hepatol, 2021;19:699–706.

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.

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

Hirano I, Moy N, Heckman M, Thomas C, Gonsalves N, Achem S. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut, 2013;62:489–95.

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

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

9. Appendices

9.1 Appendix 1: Dysphagia Symptom Questionnaire, [redacted], and EoE Endoscopic Reference Score

Dysphagia Symptom Questionnaire

Patient ID: _____ - _____ - _____

Date: _____

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

Allakos, Inc. Dysphagia Symptom Questionnaire v2.0

9.1 Appendix 1 DSQ, CCI , and EREFS cont.

The DSQ was validated with the following scoring algorithm (Hudgens, 2017).

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

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

9.1 Appendix 1 DSQ, EoEHSS, and EREFS cont.

EoE Endoscopic Reference Score (EREFS)
(Hirano, 2013)

The EREFS is the sum of 5 components with a maximum score of 9 for each location (proximal and distal esophagus) and maximum combined score of 18. Individual component score ranges are as follows:

- Edema 0–1
- Rings 0–3
- Exudates 0–2
- Furrows 0–2
- Stricture Range 0–1

Each component is scored based on the presence and/or grade of each feature. Miscellaneous features will not be included in the total score.

Improvements in inflammatory and remodeling features may also be reported based on individual scores for edema, rings, furrows, exudate, and stricture.

Inflammatory and fibrostenotic subscores will be generated (proximal, distal, and combined). The inflammatory subscore is the sum of the exudate, edema, and furrows scores (range 0–5). The fibrostenotic subscore is the sum of the rings and stricture scores (range 0–4).

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 of 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 (≤10 mg/day of prednisone or equivalent) after the screening period.

b) Initiation of systemic or swallowed corticosteroids (≤10 mg/day of 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. Any subject requiring a therapeutic EGD (defined as dilatation or other intervention for a narrowing or stricture) that may impact subsequent assessment of the DSQ during the first qualifying EGD at the end of the screening period or at any point during the study through Study Week 24.

D. 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 (≤10 mg of 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 patient-reported GI symptoms, subjects must meet the entry requirements for both histology and symptom burden (DSQ) 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 ICE. For PPI and corticosteroids (≤10 mg/day of 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 one 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 a 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 patients 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, Listings, and Figures

Tables

9.3 Appendix 3: List of Tables, Listings, and Figures cont.

Table 14.1.14	Baseline Vital Signs (MITT Population)
Table 14.1.15	Subject Incidence of Intercurrent Events (MITT Population)
Table 14.2.1.1	Tissue Eosinophil Responder at Week 24 – Primary and Sensitivity Analysis (MITT Population)
Table 14.2.1.2.1	Tissue Eosinophil Responder at Week 24 by Gender Subgroup (MITT Population)
Table 14.2.1.2.2	Tissue Eosinophil Responder at Week 24 by Age (MITT Population)
Table 14.2.1.2.3	Tissue Eosinophil Responder at Week 24 by Race Subgroup (MITT Population)
Table 14.2.1.2.4	Tissue Eosinophil Responder at Week 24 by Baseline DSQ Subgroup (MITT Population)
Table 14.2.2.1	Change from Baseline in DSQ: Primary Analysis – Multiple Imputation for Missing Biweekly DSQ (MITT Population)
Table 14.2.2.2	Change from Baseline in Weeks 23–24 DSQ Scores: Sensitivity Analysis 1 – Biweekly DSQ due to ICE are Replaced/Imputed Using Placebo-Based Pattern-Mixture Model Multiple Imputation (MITT Population)
Table 14.2.2.3	Change from Baseline in Weeks 23–24 DSQ Scores: Sensitivity Analysis 2 – Biweekly DSQ due to ICE are Replaced/Imputed Using Multiple Imputation by the Tipping Point Method (MITT Population)
Table 14.2.2.4	Change from Baseline in Weeks 23–24 DSQ Scores – Multiple Imputation (Per Protocol Population)
Table 14.2.2.5.1	Change from Baseline in Weeks 23–24 DSQ Scores by Gender Subgroup – Multiple Imputation (MITT Population)
Table 14.2.2.5.2	Change from Baseline in Weeks 23–24 DSQ Scores by Age – Multiple Imputation (MITT Population)
Table 14.2.2.5.3	Change from Baseline in Weeks 23–24 DSQ Scores by Race Subgroup – Multiple Imputation (MITT Population)
Table 14.2.2.5.4	Change from Baseline in Weeks 23–24 DSQ Scores by Baseline DSQ Subgroup – Multiple Imputation (MITT Population)

9.3 Appendix 3: List of Tables, Listings, and Figures cont.

Table 14.2.3	Percent Change from Baseline to Week 24 in Peak Esophageal Intraepithelial Eosinophil Count (MITT Population)
Table 14.2.4	Proportion of Subjects Achieving Peak Esophageal Intraepithelial Eosinophils Count ≤1 Cell/hpf at Week 24 (MITT Population)
Table 14.2.5	Subjects Achieving Peak Esophageal Intraepithelial Eosinophils Count <15 Cells/hpf at Week 24 (MITT Population)
Table 14.2.6	Subjects Achieving Peak Esophageal Intraepithelial Eosinophil and DSQ Treatment Response at Week 24 (MITT Population)
Table 14.2.7	Subjects with>50% Reduction in DSQ from Baseline to Weeks 23–24
Table 14.2.8	Percent Change from Baseline in DSQ from Baseline to Weeks 23–24 (MITT Population)
Table 14.2.9	Change in Biweekly Mean DSQ over Time Using MMRM (MITT Population)
Table 14.2.10	Change in EoE Reference Score from Baseline to Week 24 (MITT Population)
Table 14.2.11	Change in CCI [redacted] from Baseline to Week 24 (MITT Population)
Table 14.2.12.1	Change from Baseline in CCI [redacted] – Physical Component Summary (MITT Population)
Table 14.2.12.2	Change from Baseline in CCI [redacted] – Mental Component Summary (MITT Population)
Table 14.2.13	Change from Baseline to Week 24 in CCI [redacted] (MITT Population)
Table 14.2.14	Severity of Dysphagia at Baseline and Post-Baseline (MITT Population)
Table 14.2.15	Change from Baseline in Body Weight (MITT Population)
Table 14.2.16	Total Serum IgE Concentration (Per Protocol Population)
Table 14.2.17	Subject Incidence of Positive Anti-Drug (AK002) Antibody (ADA) Test (Safety Population)

9.3 Appendix 3: List of Tables, Listings, and Figures cont.

Figures

9.3 Appendix 3: List of Tables, Listings, and Figures cont.

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	Esophageal biopsy assessments (Safety Population)
Listing 16.2.2.2a	Dysphagia Symptom Questionnaire– Question Text (Safety Population)
Listing 16.2.2.2b	Dysphagia Symptom Questionnaire– Daily Score (Safety Population)
Listing 16.2.2.2c	Dysphagia Symptom Questionnaire– Biweekly Score (Safety Population)
Listing 16.2.2.3	CCI [redacted] (Safety Population)
Listing 16.2.2.4a	CCI [redacted] Questionnaire – Question Text
Listing 16.2.2.4b	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)

9.3 Appendix 3: List of Tables, Listings, and Figures cont.

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 Anti-drug (AK002) Antibody (ADA) Test (Safety Population)

Listing 16.2.3.10.1 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=DSQ seed=1357986420 nimpute=50 out=DSQ_IMPUTED1 ;
       by TRTMT ;
       class DISEASE_STRAT ;
       mcmc chain=multiple impute=full initial=em nbiter=200 niter=100 ;
var B_EOS DISEASE_STRAT B_DSQ DSQ_W01_02 DSQ_W03_04... DSQ_W21_22 DSQ_W23_24 ;
quit;
/** Recalculate change from baseline **/
data DSQ_imputed2;
   set DSQ_imputed1;
   chg=DSQ_w23_24 - b_DSQ;
run;

proc sort data=DSQ_imputed2 out=DSQ_imputed;
   by _imputation_;
run;

/** ANCOVA by imputation **/
ods output diffs=diffs lsmeans=lsm;
proc mixed data=DSQ_imputed method=reml;
   by _imputation_;
   class TRTMT;
   model CHG=DISEASE_STRAT B_DSQ 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;
```