A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Subcutaneous Lirentelimab in Adult Subjects with Moderate-to-Severe Atopic Dermatitis Inadequately Controlled by Topical Treatments

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Statistical Analysis Plan for Protocol AK002-018

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Signature Page

Prepared by:

DocuSigned by:
[redacted]
Signing Reason: I approve this document
Signing Time: 18-Sep-2023 | 07:58 PDT
[redacted], PhD
[redacted], Biometrics
Allakos, Inc.

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Date

Reviewed and Approved by:

DocuSigned by:
[redacted]
Signing Reason: I approve this document
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[redacted], MD, MBA
[redacted]
Allakos, Inc.

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List of Abbreviations

AD	Atopic dermatitis
ADA	Anti-drug antibody
ADaM	Analysis Data Model
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical (Classification System)
BLOQ	Below limit of quantification
BMI	Body mass index
CBC	Complete blood count
CDISC	Clinical Data Interchange Standards Consortium
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical study report
DM	Data management
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture (system)
ET	Early Termination
FDA	Food and Drug Administration
ICE	Intercurrent events
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IRT	Interactive Response Technology
ITT	Intent-to-treat (population)
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LSM	Least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat (population)
MMRM	Mixed Model for Repeated Measures
NRI	Non-responder Imputation

p-value	Probability value
PD	Pharmacodynamics
PE	Physical examination
PK	Pharmacokinetic(s)
PP	Per protocol (population)
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical analysis system
SC	Subcutaneous
SD	Standard deviation
SE	Standard error(s)
SDTM	Study Data Tabulation Model
SOC	System organ class
TEAE	Treatment-emergent adverse event(s)
TEAESI	Treatment-emergent adverse event(s) of special interest
TESAE	Treatment-emergent serious adverse event(s)
TLF	Tables, listings, and figures
ULN	Upper limit of normal
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

Revision History

Version Date	Version Number	Description
25 July 2023	**1**	Initial document
18 September 2023	**2**	Amendment 1

1. Introduction

Lirentelimab (AK002) Subcutaneous (SC) is being studied in subjects with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments. Atopic dermatitis (AD) is a chronic pruritic inflammatory dermatitis that affects approximately 16.5 million (7.3%) adults in the US, of which around 6.6 million (40%) have moderate-to-severe disease.

The statistical analysis plan (SAP) describes *a priori* the data and variables to be summarized or analyzed, including specifications of the analytical methods to be performed. This SAP supersedes the statistical analysis methods described in the clinical protocol except for the standard pharmacokinetic (PK) data analyses. Significant deviations/changes from the planned analyses described in this SAP will be identified, with justification, in the appropriate section of the clinical study report (CSR). The SAP is based on Clinical Study Protocol AK002-018 Amendment 6, dated 08 September 2023, and the associated electronic case report form (eCRF).

2. Study Objectives

2.1 Primary Objective and Endpoint

The primary objective of the study is to assess the efficacy of lirentelimab SC in subjects with moderate-to-severe AD as assessed by the difference in the proportion of subjects who achieve at least 75 percent improvement from baseline in the Eczema Area and Severity Index (EASI-75) at Week 14 when compared with placebo.

In particular, the associated estimand for this objective is to measure the effect of therapy with lirentelimab SC as assessed by the proportion of subjects with EASI-75 response at Week 14 assuming treatment response disappears after subjects are rescued or discontinue from the study or treatment. See Sections 4.2.5 and 6.9.1 on how this estimand handles outcomes after the occurrence of any intercurrent event through non-responder imputation (NRI).

2.1.1 Eczema Area and Severity Index (EASI)

The EASI score is a tool used to measure the extent (area) and severity of atopic dermatitis with respect to erythema, excoriation, induration, and lichenification over the 4 anatomic regions of the body: lower and upper extremities, trunk, and head. The total EASI score will be in a range from 0 to 72 points (from no disease to maximum disease severity) and the assessment is conducted by the Investigator. An EASI score of ≥16 during screening is required to enroll in the study. The EASI will be determined by Investigators at the scheduled and unscheduled clinic visits according to Table 1.

Enrollment will be monitored to limit the impact of randomizing a disproportionately large number of subjects with an EASI score in the lower range, reflecting more moderate disease only (i.e., EASI score < 22). This will also provide a subject population with a full range of EASI scores consistent with the intent to study lirentelimab in moderate-to-severe AD disease.

2.2 Secondary Objectives and Endpoints

The secondary objectives are to characterize further the efficacy of lirentelimab SC in subjects with moderate-to-severe AD as measured by:

- Percent change in EASI from baseline to Week 14
- Proportion of subjects with IGA of 0 or 1 and a 2-point improvement at Week 14 compared with baseline

2.2.1 Investigator's Global Assessment (IGA)

The Investigator's Global Assessment (IGA) is a 5-point scale that provides a global clinical assessment of AD severity ranging from 0 to 4 and assesses disease severity and clinical response using a 5-point scale: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; and 4 = severe. The score is determined by ranking the extent of erythema and papulation/infiltration. A decrease in score relates to an improvement in signs and symptoms. The IGA will be determined by Investigators at the scheduled and unscheduled clinic visits according to Table 1.

2.3 Exploratory Objectives and Endpoints

The exploratory objectives are to evaluate the effect of lirentelimab SC in subjects with moderate-to-severe AD for the following parameters:

- Change in [redacted] at Week 14.
- Time to onset of response on the [redacted], where response is defined as improvement (at least a [redacted] reduction from baseline) of weekly average of daily [redacted] during the 14-week treatment period. The analysis will be based on subjects with a baseline [redacted]
- Change from baseline to Week 14 in [redacted].
- Pharmacodynamics (PD) of lirentelimab SC in subjects with AD as measured by changes from baseline in [redacted]
- Other indices of efficacy of lirentelimab SC in subjects with AD. Changes in signs and symptoms (compared to baseline) between lirentelimab SC and placebo will be measured by:

- Change from baseline to Week 14 in [redacted]
- Change in [redacted] from baseline to Week 14
- Proportion of subjects who achieve [redacted]
- Proportion of subjects who achieve [redacted]
- Change from baseline to Week 14 in [redacted]
- Change from baseline to Week 14 in [redacted]
- Change from baseline over time in [redacted]

2.3.1 [redacted]

The [redacted] is a clinical tool used to determine the [redacted]. The [redacted] tool was developed by the [redacted] as a measure of [redacted]. It includes assessment of the [redacted] by the Investigator in addition to patient-reported symptoms. Subjective assessment of [redacted] is recorded for each symptom by the patient on a [redacted] where [redacted] and [redacted]. Total score ranges from [redacted]. During screening, [redacted] will be determined, and a baseline will be established. In addition, [redacted] will also be determined predose on all dosing days and during follow-up on Days 99, 141, and 169 or ET.

2.3.2 [redacted]

The [redacted] is a validated [redacted], patient reported outcome (PRO) of [redacted] that will be completed by the subject on a daily basis, at approximately the same time every day. On dosing days, [redacted] should be completed while subject is at the site.

During screening, [redacted] will be determined, and a baseline will be established. The [redacted] rating system captures the [redacted] over a 24-hour period. The following question will be presented to subjects:

[redacted]

Scale of [redacted]

2.3.3 [redacted]

The [redacted] is a simple measurement of the [redacted]. At screening, the Investigator will determine the [redacted]. The subject is [redacted] to enroll in the study. The [redacted] will be determined by the Investigator during screening, predose on all dosing days, and during follow-up on Days 99, 141, and 169 or ET.

2.3.4 [redacted]

The [redacted] is a [redacted] questionnaire used to measure the impact of [redacted] of an affected person. The format is a simple response [redacted] that assess [redacted] over the past week with an overall scoring system of [redacted] a high score is indicative of a [redacted] is a self-administered- questionnaire. Subjects will complete this during screening, predose on all dosing days, and during follow-up on Days 99, 141, and 169 or ET.

2.4 Safety Objectives and 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, serious adverse events (SAE), and adverse events (AE) leading to study drug withdrawal
- Anti-drug (AK002) antibody (ADA)
- Changes in Laboratory tests
- Changes in Physical examination
- Changes in vital signs

3. Study Design

3.1 General Description

This Phase 2, proof-of-concept, randomized, double-blind, placebo-controlled study will investigate the efficacy and safety of lirentelimab SC in adult subjects with moderate-to-severe AD inadequately controlled by topical treatments. Approximately 130 subjects will be enrolled in approximately 70 sites in the US and Germany and will be randomized 1:1 to receive either 7 SC injections of placebo or lirentelimab and then followed for 12 weeks after the last dose. Subjects will be given the option to enroll into an open-label extension (OLE) period of the study after completing the Day 99 visit of the double-blind period. Subjects choosing not to enter the

OLE period will continue to be followed in the double-blind period of the study for 12 weeks after the last dose.

Based on the feedback from atopic dermatitis experts and completed feasibility assessments, it is expected that each site will be able to screen three subjects and enroll two of them in the duration of the enrollment period. Enrollment is competitive, and to ensure the enrollment goal is achieved in a timely manner, approximately 70 sites (approximately 55 in the US and approximately 15 in Germany) will be initiated. If study enrollment rate can be achieved with fewer sites to meet the study timeline, then fewer sites may be needed.

Subjects will be consented and screened, and those 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 patient identification number and rescreened once. Subjects rescreened within 30 days of signing the initial informed consent form (ICF) will not need to sign a new ICF if there have been no changes to the ICF.

Subjects will be screened for approximately 2 weeks (-14 days) prior to dose administration. During screening and through various time points during the study, the EASI, IGA, BSA, peak pruritus Numeric Rating Scale (ppNRS), Scoring Atopic Dermatitis Index (SCORAD), and Dermatology Life Quality Index (DLQI) assessments will be completed. Additional questions will be asked about symptoms related to asthma, allergic rhinitis, and allergic conjunctivitis that subjects with the atopic condition(s) may have on Day 1, Day 99, and OLE Day 99 (Atopic Conditions Questionnaire).

Certain medications are prohibited during the study. Use of systemic and/or topical corticosteroids, calcineurin inhibitors, JAK inhibitors, topical PDE4 inhibitors (crisaborole), dupilumab, or tralokinumab are prohibited during the study. Subjects who are on any topical corticosteroids, topical calcineurin inhibitors, topical JAK inhibitors, or PDE4 inhibitors at the time of screening must discontinue these at the first screening visit.

Biologics or medications that may interfere with the study safety or efficacy assessments such as systemic immunosuppressive or immunomodulatory drugs or biologics and systemic corticosteroids must be discontinued prior to the first screening visit and are prohibited throughout the study.

During the last 7 days prior to Day 1 (the first day of study drug dosing), the subject must have used, at least twice daily, only non-medicated topical therapy (i.e., emollient) without other active ingredients indicated to treat AD or other additives, which could affect AD (e.g., hyaluronic acid, urea, ceramide, or filaggrin degradation products). If a subject is not using any

emollient at the time of screening, a suitable non-medicated, non-prescription emollient will be recommended by the Investigator.

Eligible subjects who meet selection criteria at screening and at baseline will receive the first dose of lirentelimab SC or placebo SC on Day 1. Subjects will receive 6 more doses on Days 15, 29, 43, 57, 71, and 85.

Subjects will be given the option of entering an OLE period of the study after completing the Day 99 visit of the double-blind period of the study, contingent on meeting defined study selection criteria. Subjects not entering the OLE period will be followed for 12 weeks after the last dose in the double-blind period.

The primary endpoint will be assessed at Week 14, i.e., 2 weeks following the last dose in the double-blind period of the study.

Randomization will be stratified based on IGA 3 vs. 4 and on biologic status as it pertains to previous treatment of atopic dermatitis, naïve vs. exposed. Approximately 40% of the study population will be subjects with an IGA of 4.

Fresh biopsies of lesional and non-lesional skin may be collected from subjects predose and post-dose at selected US sites. Providing biopsies is optional, and subjects will sign a separate consent form for biopsy collection.

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

Table 1 Schedule of Assessments

Assessment/Procedure Description	Screening	Double-Blind Treatment Period (12 weeks)								Follow-Up Period (12 weeks)		
	~Day -14 (2 weeks)	Day 1[1] (±3 days) Baseline	Day 8 (±3 days)	Day 15 (±5 days)	Day 29 (±5 days)	Day 43 (±5 days)	Day 57 (±5 days)	Day 71 (±5 days)	Day 85 (±5 days)	Day 99 (±5 days)	Day 141 (±5 days)	Day 169 (±5 days)
	Week -2	Week 0/ **Dose 1**	Week 1 Visit	Week 2/ **Dose 2**	Week 4/ **Dose 3**	Week 6/ **Dose 4**	Week 8/ **Dose 5**	Week 10/ **Dose 6**	Week 12/ **Dose 7**	Week 14/ Follow-up 1	Week 20/ Follow-up 2	Week 24/ Follow-up 3/EOS[2]
Informed consent	X											
Demographics	X											
Medical History	X	X										
Detailed previous diagnosis and treatments review[3]	X											
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height[4]	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[5]	X	X	X	X	X	X	X	X	X	X	X	X
10-lead or 12-lead ECG[6]	X											
Complete physical exam[7]	X											
Symptom-directed physical exam[7]		X	X	X	X	X	X	X	X	X	X	X
vIGA score and dermatologic assessment[9]	X	X		X	X	X	X	X	X	X	X	X
EASI[9]	X	X		X	X	X	X	X	X	X	X	X
[redacted][9]	X	X		X	X	X	X	X	X	X	X	X
[redacted][9]	X	X		X	X	X	X	X	X	X	X	X
[redacted][8,9]	<----------Complete daily from screening through Day 169 or 84 days post last dose---------->											
[redacted][9]	X	X		X	X	X	X	X	X	X	X	X

Assessment/Procedure Description	Screening	Double-Blind Treatment Period (12 weeks)								Follow-Up Period (12 weeks)		
	~Day -14 (2 weeks)	Day 1[1] (±3 days) Baseline	Day 8 (±3 days)	Day 15 (±5 days)	Day 29 (±5 days)	Day 43 (±5 days)	Day 57 (±5 days)	Day 71 (±5 days)	Day 85 (±5 days)	Day 99 (±5 days)	Day 141 (±5 days)	Day 169 (±5 days)
	Week -2	Week 0/ Dose 1	Week 1 Visit	Week 2/ Dose 2	Week 4/ Dose 3	Week 6/ Dose 4	Week 8/ Dose 5	Week 10/ Dose 6	Week 12/ Dose 7	Week 14/ Follow-up 1	Week 20/ Follow-up 2	Week 24/ Follow-up 3/EOS[2]
Atopic Conditions Questionnaire[10]		X								X		
Blood for total serum IgE[11]	X						X		X	X	X	X
Blood for serology [12]	X											
Blood for chemistry (includes hCG and FSH screening only)[13]	X	X		X	X	X	X	X	X	X	X	X
Blood for CBC with differential[14]	X	X		X	X	X	X	X	X	X	X	X
Blood for PK[15]		X	X	X	X	X	X	X	X	X	X	X
Blood for ADA[16]		X	X			X			X	X		X
Urine for dipstick pregnancy test[17]		X	X	X	X	X	X	X	X	X	X	X
Urine for urinalysis[18]	X									X		X
Eligibility assessment	X	X										
Access IRT: Stratification and randomization and kit assignment[19]		X										
Study drug administration		X		X	X	X	X	X	X			
Non-serious adverse events[20]		X	X	X	X	X	X	X	X	X	X	X
Serious adverse events[21]		X	X	X	X	X	X	X	X	X	X	X
Biopsies (Optional) [22]		X								X		
Begin OLE period of the study after Day 99 assessments (if applicable)[23]											Day 141–169 visits are not applicable for OLE subjects	

ADA: Anti-lirentelimab antibody
[redacted]
CBC: Complete Blood Count
[redacted]
EASI: Eczema Area and Severity Index
ECG: Electrocardiogram
EOS: End of Study
FSH: Follicle-Stimulating Hormone
hCG: Human Chorionic Gonadotropin
IgE: Immunoglobulin E
IP: Investigational Product
IRT: Interactive Response Technology
PK: Pharmacokinetics
[redacted]
vIGA: Validated Investigator's Global Assessment

Table 1 Notes

1) Dose 1 is the day of the first SC injection. Dose 1/Day 1 can occur within a ±3 day window, i.e., the screening period can be a maximum of 17 days and a minimum of 11 days. Dosing visits must be conducted within the ± windows stipulated in the protocol.

2) The EOS visits should be conducted 14, 56, and 84 (±5) days after the last dose of study drug or prior to this, if necessary, to ensure compliance with the visit. If the EOS visit occurs more than 56 days after the last dose of study drug, then perform the visit as soon as possible. The procedures listed under the 14-day post-study drug visit will be conducted unless otherwise directed by the Medical Monitor. For subjects participating in the OLE period, AE and concomitant medications should be collected and recorded in the AK002-018 double blind treatment period database up until the start of the first open-label SC injection after the Day 99 visit.

3) Documentation of AD diagnosis and previous treatments should be noted in detail. This can be subject reported and/or based on medical records (details in protocol Section 12.2.6).

4) At screening, height (in cm) and weight (in kg) will be recorded. Body weight will be measured at every visit.

5) Vital signs will be measured at every visit. On all dosing days: within 30 minutes predose, 15 (±5) minutes after administration of study drug SC injection, and just prior to discharge. Additional vital sign measurements may be collected at the Investigator's discretion if an injection-related reaction (IRR) occurs. Vital signs including systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate will be measured after the subject has been at rest for ≥5 minutes and before any blood draws have been obtained (unless collected for an IRR).

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

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

8) Activate PRO questionnaire and provide subject with unique username and password. PRO questionnaire should be activated for all subjects on screening Day 1.

9) During screening, vIGA, EASI, [redacted] will be determined, and a baseline will be established. vIGA, EASI, [redacted] must be completed predose on dosing days. To ensure there is sufficient PRO data at baseline, a subject should complete at least four daily PRO questionnaires per week for a minimum period of the seven days prior to Day 1.

Table 1 Notes cont.

10) Subjects will be prompted to answer additional questions about symptoms related to asthma, allergic rhinitis, and allergic conjunctivitis (Atopic Conditions Questionnaire).

11) Blood samples for total serum IgE will be collected during screening, predose on Days 57 and 85, on follow-up Days 99, 141, and 169, or 14, 56, and 84 (±5) days after the last dose of study drug if early termination (ET).

12) Blood for serology testing will be collected during screening and will include HBsAg, hepatitis C antibody, anti-HBc, and HIV.

13) Female subjects of childbearing potential are required to have hCG measured. Postmenopausal women are required to have FSH measured. If FSH result is ≤30 mIU/mL, a negative serum hCG will be required during the screening period in order for subject to proceed to randomization. Blood for chemistry will be obtained predose on dosing days and follow-up days (14, 56, and 84 [±5] days after the last dose of study drug if ET).

14) Blood for CBC with differential, including absolute blood eosinophil count, will be obtained at screening, just prior to each SC injection, 1 hour (±15 minutes) after the end of each SC injection, and on all follow-up days (14, 56, and 84 [±5] days after last dose if ET). All differential blood counts from Day 1 (post-dose) through the end of the subject's participation in the double-blind period will be blinded to the Sponsor and the site. An unscheduled CBC may be collected at the request of the Safety Monitor.

15) Blood for PK will be obtained predose on all dosing days as well as on Day 8 (±3) and on follow-up days (14, 56 and 84 [±5] days after last dose of study drug if ET).

16) Blood for ADA will be collected predose on dosing Days 1, 43, and 85 (±5), as well as on Day 8 (±3), and on follow-up Days 99 and 169 (14 and 84 [±5] days after last dose of study drug if ET). The ADA sample will also be collected any time an immunogenicity-related AE occurs.

17) Urine will be collected for dipstick pregnancy test on all dosing days, Day 8, and all follow-up days (14, 56, and 84 days after last dose of study drug if ET) for all subjects of childbearing potential. Test kits will be supplied by the central laboratory. Tests will be completed on site and evaluated prior to each SC injection.

18) Urine for standard urinalysis will be obtained at screening and on follow-up Days 99 and 169 (14 and 84 days [±5] if ET), and symptom-based, as necessary.

19) Randomization will be conducted through the IRT system. Subjects will be randomized 1:1, lirentelimab SC 300 mg or placebo SC. They will be stratified based on biologic status and IGA score at baseline.

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

21) The reporting of serious adverse events (SAE) occurring after signing the ICF and prior to the first SC injection will be limited to those that relate to screening procedures. The capture of all SAE and AE that are not related to screening procedures will begin at the time of first SC injection of study drug. For subjects participating in the OLE period, AE will be assessed and recorded in the CRF of the AK002-018 double-blind treatment period database up until the start of the first OLE SC injection, after the Day 99 visit. The AE will be recorded in the CRF of the AK002-018 OLE period database beginning with the start of the first open-label SC injection after Day 99.

22) Lesional and non-lesional biopsies will be collected at selected US sites and only for subjects who consent to this optional procedure. Biopsies may be collected at baseline predose on Day 1 and again on Day 99/Week 14. See Section 12.1.10 of the protocol.

Table 1 Notes cont.

23) Open-label extension dosing may start on Day 99 after all Day 99 procedures are conducted or within 7 days after the Day 99 visit. Subjects who decide to enter the OLE period and meet the selection criteria for the OLE period, will follow the schedule of events in Appendix 11 of the protocol and do not need to repeat Day 99 procedures if OLE Day 1 visit is completed on the same day as Day 99 visit.

3.2 Methods of Assigning Subjects to Treatment Groups

Approximately 130 subjects with moderate-to-severe AD inadequately controlled by topical treatments will be randomized to lirentelimab SC, or placebo in a 1:1 ratio. Stratified permuted block randomization will be used. Randomization will be stratified based on IGA 3 vs. 4 and on biologic status, naïve vs. exposed. Approximately 40% of the study population will be subjects with an IGA of 4. An Interactive Response Technology System (IRT) will be used to perform the randomization.

3.3 Treatment Blinding

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

3.4 Determination of Sample Size

It is hypothesized that the percentage of subjects who achieve EASI 75 at Week 14 are 44% and 15% for lirentelimab SC and placebo SC, respectively.

To detect a treatment difference of 29%, the number of subjects required for 90% power is 55. However, to account for an anticipated 10% dropout rate, the sample size will be increased to 65 per treatment group.

Enrollment will be monitored to limit the impact of randomizing a disproportionately large number of subjects with an EASI score in the lower range, reflecting more moderate disease only (i.e., EASI score <22). This will also provide a subject population with a full range of EASI scores consistent with the intent to study lirentelimab in moderate-to-severe AD disease.

4. Definitions

4.1 Terminology and Definitions

Table 2 Terminology and Definitions

Terminology	Definition
Baseline	Baseline for non-daily assessment (e.g., laboratory tests) is defined as the non-missing value collected most recently to and before the time of the very first dose of study drug. Baseline Patient Reported Outcome (PRO) data will be the average of the weekly PRO data collected in the last 7 days prior to Day 1.
Concomitant Medications and Procedures	Medications and procedures with a stop date before the treatment dosing date will be considered prior medications/procedures. Medications/procedures with a start or stop date on or after the treatment dosing date will be considered concomitant. All medications/procedures marked as ongoing are concomitant.
Study Day	Study Day 1 is defined as the date on which a subject received the first dose of study drug. 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 Week	Study Week for PRO analysis is defined as 7 days a week starting from the day of first dose (Day 1).

4.2 Target of Estimation

The estimand for the AK002-018 study estimates the effect of treatment, while considering treatment adherence and response. The estimand will provide an answer to the question that is crucial to individual subjects: "If I take this study medication as part of my treatment regimen, without adding any further drugs or exit the study prematurely, what improvement can I expect at 14 weeks?"

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

4.2.1 Population Targeted by the Scientific Question

The population targeted by the scientific question is defined via the inclusion and exclusion criteria as part of the study protocol. Subjects may be male or female and must have a clinical diagnosis of moderate-to-severe AD inadequately controlled by topical treatments of sufficient duration within the 6-month period prior to study entry as defined by the study inclusion criteria.

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

The primary endpoint is the proportion of subjects who achieved EASI-75 in Week 14.

4.2.3 Treatment

Lirentelimab SC or placebo SC administered to subjects on Days 1, 15, 29, 43, 57, 71, and 85.

4.2.4 Intercurrent Events

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

- Premature discontinuation from the double-blind portion of the study
- Use of prohibited medications during the study
- Use of rescue medication for symptoms of AD

4.2.5 Strategy for Handling Intercurrent Events

For subjects who experienced an ICE of premature discontinuation from the double-blind portion of the study, efficacy outcome will be defined as “non-responder” for binary endpoints and will be set to missing for continuous endpoints from the point when that ICE occurs. An appropriate method for handling missing data through statistical modeling (e.g., multiple imputation [MI]) will be used.

For subjects that take prohibited medications during the double-blind portion of the study (see Appendix 1: Intercurrent Events and Definitions of Prohibited Medication Use and Rescue Medication/Treatment for AD Symptoms) for medically necessary reasons other than alleviating AD symptoms, the efficacy data will be handled as follows:

- The use of topical corticosteroids, topical calcineurin inhibitors, topical JAK inhibitors, topical PDE4 inhibitors or other prohibited topical medications for reasons other than for the treatment of AD for 5 or more days will result in all subsequent efficacy data being censored for purposes of analysis from the time of initiation of the prohibited therapy onwards. Use of prohibited topical therapies for a duration of less than 5 days will result in

all subsequent efficacy data being censored for purposes of analysis from the time of initiation of the prohibited therapy onwards only if the treatment occurs within 7 days of the Day 99 visit.

- The use of systemic corticosteroids for periods of 3 or more days or the use of depot injectable steroids for medical reasons other than the treatment of AD will result in all subsequent efficacy data being censored for purposes of analysis from the time of initiation of the prohibited therapy onwards. Use of systemic corticosteroids for a duration of less than 3 days will result in all subsequent efficacy data being censored for purposes of analysis from the time of initiation of the prohibited therapy onwards if the treatment occurs within 28 days of the Day 99 visit.
- The use of any other systemic immunomodulator (including JAK inhibitors), immunosuppressant or biologic therapy during the course of the study for the purpose of treating a medical condition other than AD will result in censoring of all efficacy data from the time of initiation of the prohibited therapy onwards.

When applicable, the censoring rule will censor data after a subject experiences an ICE. This censoring rule is equivalent to using all the data up to the date of an ICE.

For subjects that take prohibited medications during the double-blind portion of the study (see Appendix 1: Intercurrent Events and Definitions of Prohibited Medication Use and Rescue Medication/Treatment for AD Symptoms) described as either rescue therapy or taken for the purpose of alleviating AD symptoms the efficacy data will be handled as follows:

The use of rescue therapy for the treatment of AD symptoms defined as either 1) use of topical corticosteroids, topical calcineurin inhibitors, JAK inhibitors, topical PDE4 inhibitors or other prohibited topical therapies at any point in the study, 2) the use of phototherapy for AD, 3) the use of systemic corticosteroids (including injectables) for the treatment of AD or 4) the use of any systemic immunomodulator (including JAK inhibitors), immunosuppressant or biologic therapy at any point in the study will result in that subject being considered as having an ICE and efficacy data will be imputed as a non-responder from the time of initiation of the rescue therapy onwards.

Blinded adjudication of all potential ICE due to either prohibited medication use for any medical reason or use of rescue medications for symptoms of AD will be implemented before database locks.

4.2.6 Summary Measure of the Estimand

Percent (and 95% CI) of subjects achieving EASI-75 at Week 14 in the lirentelimab SC and Placebo treatment groups and the absolute difference (and 95% CI) in the percent response between treatments.

5. Statistical Methods

5.1 General Methodology

All statistical analyses will be conducted using SAS v9.4 or later version on the Microsoft Windows Operating System.

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

Continuous data will be summarized using "n" (number of subjects with non-missing observations), mean, median, standard deviation (SD), minimum value, and maximum value. Categorical data will be summarized using the frequency count and percentage (n, %) of subjects in each category. Number of subjects with non-missing values or number of subjects with missing values (e.g., Not Done) will be presented, where appropriate. Subjects with missing values will not contribute to the denominator for percentage calculations, unless specified otherwise. Counts of 0 in any category will be presented without percentage. All summaries will be presented for individual treatment groups. In addition, for summary of disposition and subject baseline characteristics, the presentation will include both treatment groups combined.

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

- Sample size (n, N) and number of missing responses (if displayed): Integer
- Mean, confidence interval, and median: Same number of decimal places as reported/collected
- Standard deviation: Same number of decimal places as reported/collected
- Percentiles, minimum, maximum: Same number of decimal places as reported/collected
- Odds Ratio: 2 decimal places

- Percentage: 1 decimal place generally, or 2 decimal places for <0.1%, or no decimal places for 0% and ≥100%
- P-value: 4 decimal places
- WBC: 2 decimal places as 0.01×10^9/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, and reason for departure from the planned methods will be documented in 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. Assessments will be slotted into analysis windows to allow summaries to be performed for subjects with similar study drug exposure. The analysis windows are described in Table 1 by the target study days (see Table 2) of the planned visits. For example, for visit description Day 8, the window is ±3 days of the visit description.

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

eDiary daily results (ppNRS) will be summarized by Study Week as outlined in Table 2.

5.3 Adjustment for Covariates

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

5.4 Data Handling Conventions

This section includes the methods for missing data imputation for some summary analyses, if necessary.

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 Independent Safety Monitoring and Interim Data Analysis

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

No interim analysis will be conducted for this study.

5.6 Timing of Data Analyses

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

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

- All records are entered in the database.
- All AE are coded to the satisfaction of the Chief Medical Officer.

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

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

5.7 Multicenter Study

The study will have approximately 70 sites in the US and Germany. For efficacy analysis, sites within countries will be pooled together.

5.8 Multiple Comparisons/Multiplicity Adjustment

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

Test primary efficacy endpoint at 2-sided α=0.05 level.

- If $p \leq 0.05$ for primary endpoint, then reject the null hypothesis that lirentelimab SC is no different from placebo and accept the alternative hypothesis that lirentelimab SC is superior to placebo in improving EASI score.
- If $p \leq 0.05$ for primary endpoint, the hypothesis tests for the secondary endpoints will proceed in the prespecified order (see Section 2.2). If at any point during the analysis of the secondary endpoints, the statistical test is not significant at 2-sided α=0.05 level, the hypothesis testing procedure will stop. Lirentelimab SC will be deemed superior to placebo for all endpoints prior to the stop.

5.9 Examination of Subgroups

Key endpoints will be summarized by subgroup to assess the consistency of the treatment effect across each of these subgroups. For any subgroup, if there are zero subjects within a stratification stratum in any treatment group, the statistical model will not be adjusted by the stratification factors. Subgroups to be considered are:

- Sex (Male, Female)
- Age group (<65, ≥65)
- Race (White, Non-White)
- Age of disease onset (<18 years, ≥18 years)
- Baseline disease severity index [moderate (IGA=3) and severe (IGA=4)]
- Baseline EASI severity index [moderate (EASI score <22) and severe (EASI score ≥22)]
- Body Surface Area (BSA) (≥10% - <16%, ≥16%-<40%, ≥40%)
- Prior biologics experience for the treatment of atopic dermatitis (biologic-naïve and biologic-exposed)

6. Statistical Analysis

6.1 Analysis Populations

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

6.1.1 Safety Population

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

6.1.2 Intent-to-Treat Population

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

6.1.3 Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population will be defined as all randomized subjects who received at least one SC injection of study drug and had no major protocol violations based on key inclusion and exclusion criteria defining the population of interest (i.e., defined as not meeting any of the key inclusion criteria number 3, 4, 6, 7, 8 or meeting exclusion criteria number 8 in this study).

To assess the impact of excluding subjects from the efficacy analyses, results including all subjects (this population will be referred to as All Subjects All Data) and excluding the subjects who had any major protocol violation based on key inclusion and exclusion criteria defining the population of interest will be presented. The differences between these results will be noted, and the impact of such differences will be discussed in the clinical study report.

6.1.4 Per Protocol Population

The per protocol (PP) population will include the subjects in the mITT population who do not have any major protocol deviations or violations and who receive all 7 injections of study drug (see Section 6.3 for list of protocol deviations and violations).

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 the ITT population. 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 the ITT population.

6.3 Protocol Deviations and Violations

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 8.5)
- Any major violations of efficacy-related entry inclusion or exclusion criteria (defined as not meeting inclusion criteria number 3, 4, 6, 7, 8 or meeting exclusion criteria number 8)
- 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 mITT and PP population will be listed with reasons for exclusion.

6.4 Demographics and Baseline Disease Characteristics

The following demographic and baseline characteristics variables will be summarized:

- Demographic variables: Age at screening (year), age group, sex, ethnicity, race, baseline weight (kg) with grouping (<60 kg, ≥60 kg), BMI (kg/m2) with grouping (<20, ≥20)
- Baseline characteristics: Age of disease onset with grouping (<18 years, ≥18 years), peak pruritus numerical rating scale (ppNRS), Investigator's Global Assessment (IGA) score, Eczema Area and Severity Index (EASI) score, SCORing Atopic Dermatitis (SCORAD) score, Body Surface Area (BSA) affected by AD, Dermatology Life Quality Index (DLQI)

Descriptive statistics for these variables 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 Medical History

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

6.6 Electrocardiogram

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

6.7 Pregnancy Test

A listing of pregnancy test results will be provided.

6.8 Treatments

6.8.1 Treatment Compliance

Summaries of treatment compliance will be based on the safety population.

The compliance with study treatment will be calculated as follows:

Treatment Compliance = (Number of study drug injections during exposure period)/ (Number of planned study drug injections during exposure period) x 100%.

The treatment compliance will be presented by the following specific ranges for each treatment group: <80%, and ≥80%.

In addition, an overall compliance that includes adherence to treatment administration schedule and any interruptions will be included in the data listing.

6.8.2 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 the WHO Drug Dictionary (WHODD March 2018 release) for preferred term (PT) and Anatomical Therapeutic Chemical (ATC) classification.

Medications will be tabulated separately based on the Safety population. The number (n and %) of subjects taking at least 1 medication and the number (%) of subjects taking each medication at the preferred term level will be tabulated by ATC4, and PT. Subjects taking the same PT medication twice will only be counted once.

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

6.9 Analyses of Efficacy Endpoints

For all efficacy variables, the analysis will be comparison of lirentelimab SC and the placebo treatment groups. The following null and alternative hypotheses for the primary endpoint will be tested for lirentelimab SC group and the placebo group:

H_0: No treatment difference between lirentelimab SC and placebo

H_1: There is a treatment difference between lirentelimab SC and placebo

Baseline disease severity index [moderate (IGA=3) and severe (IGA=4)] and prior biologic experience (biologic-naïve and biologic-exposed) will be the 2 stratification factors for subject randomization and will be accounted for in the statistical modeling for efficacy. In addition, if it

is evident that the primary endpoint is confounded by study entry characteristics [e.g., the method of IGA and/or EASI score assessment by AD specialist (defined as the PI and or Sub-I being either an allergist, immunologist or dermatologist) as compared to non-AD specialist, change in percent BSA greater than 20% at the end of the Lead-in Phase (Day -14 to Day -8) compared to the end of the Baseline Phase (Day -7 to Day -1)], then the primary efficacy analysis will be conducted adjusting for the effects of the background characteristics.

6.9.1 Analysis of Primary Efficacy Endpoint

The primary responder endpoint will be analyzed using the Cochran-Mantel-Haenszel test adjusted by baseline disease severity index [moderate (IGA=3) and severe (IGA=4)], prior biologic experience (biologic-naïve and biologic-exposed), and country (USA and Germany) at Week 14. A sample SAS code 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 DISEASE_INDEX*BIOLOGIC_EXPERIENCE*COUNTRY*TRTP*RESP /
cmh(MF) commonriskdiff
(cl=NEWCOMBE) ;
run ;
```

The Mantel-Fleiss (MF) criterion will be performed, and if it is not met while using the option CMH (MF) in SAS procedure PROC FREQ, analyses including each factor separately in CMH test will be conducted. Should assumption per the MF criterion not be satisfied, the comparison will be based on a Fisher's exact test after collapsing across levels of the stratification factor and country.

Below is an example of the SAS code for the Fisher's exact test:

```
* 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 TRTP ;
run;
```

For the analysis described above, subjects who prematurely discontinue the randomized treatment or initiate any treatment adjustments (e.g., use of prohibited/rescue medication/rescue treatment for AD symptoms) will be handled as described below:

- If a subject withdraws from the study, this subject will be counted as a non-responder for the time points after withdrawal
- To account for the impact of prohibited/rescue medication/rescue treatment for AD symptoms on the efficacy effect: if rescue medication/rescue treatment for AD symptoms is used (see Appendix 1: Intercurrent Events and Definitions of Prohibited Medication Use and Rescue Medication/Treatment for AD Symptoms for definitions of ICE and listings of prohibited medications and rescue medications/therapies), the subject will be specified as a non-responder from the time the rescue medication/rescue treatment is used
- If the subject has the missing value at Week 14, it will be counted as a non-responder at Week 14

The primary efficacy analysis will be performed on the mITT population, as well as PP population as a supporting analysis. In addition, for completeness purposes, results including all subjects and excluding the subjects who had major protocol deviations on the basis of key inclusion and exclusion criteria defining the population of interest will be presented. The differences between these results will be noted, and the impact of such differences will be discussed in the clinical study report.

6.9.2 Analysis of Secondary Efficacy Endpoints

The binary secondary efficacy endpoint will be analyzed using the same approaches as that are used for the analysis of the primary endpoint.

Mixed Model for Repeated Measures (MMRM) analyses will be performed on continuous endpoints to mitigate the impact of missing data. This approach assumes missing observations are missing at random and borrows information from subjects in the same treatment group, taking into account the missingness of data through the correlation of the repeated measurements.

All continuous endpoints will utilize MMRM after applying the primary censoring rule, i.e., the rule will censor data after permanent study drug discontinuation or after rescue therapy. This censoring rule is equivalent to using all the data up to discontinuation or rescue.

The MMRM model will include fixed effects for baseline value, disease severity group, biologic-naïve vs biologic-exposed, country, treatment, study week, the treatment-by-week interaction, and the baseline-by-week interaction and allow for random subject effects. Treatment and week will each be fitted as categorical variables. The model will assume unstructured covariance structure. If the model with unstructured covariance does not converge, then other covariance

structures will be considered to model the within-subject errors. The Kenward-Rogers approach for computing denominator degrees of freedom will be used to account appropriately for pooling of within-subject and between-subject variance estimates. Efficacy data on subjects who prematurely discontinue the randomized treatment or initiate any treatment adjustments (e.g., use of prohibited/rescue medication/rescue treatment for AD symptoms) will be set to missing at the designated time points after withdrawal or after the start of such treatment changes. The LSM and 95% CI for the difference between groups will be estimated using the simple contrast at each time point. Below is an example of the SAS code for the MMRM:

```
proc mixed data=EASI method=reml;
   class TRTP USUBJID AVISITN COUNTRY DISEASE_INDEX
BIOLOGIC_EXPERIENCE;
   model PCHG= B_EASI TRTP AVISITN COUNTRY DISEASE_INDEX
BIOLOGIC_EXPERIENCE TRTP*AVISITN B_EASI*AVISITN / DDFM=KR;
REPEATED AVISITN / SUBJECT=USUBJID (TRTP) TYPE=UN;
RANDOM COUNTRY;
LSMEANS TRTP*AVISITN / PDIFF CL;
RUN;
```

Where TRTP = planned treatment group in numeric (1 = placebo, 2 = lirentelimab SC); AVISITN = time point (i.e., Weeks 2, 4, 6, 8, 10, 12, and 14).

6.10 Analysis of Exploratory Endpoints

6.10.1 Change from Baseline in [redacted]

The endpoint will be analyzed using the same approaches as that are used for the analysis of the secondary efficacy continuous endpoint of percent change in EASI.

6.10.2 Time to Onset of Response on [redacted]

Time to onset of effect on [redacted] as measured by proportion of subjects with [redacted] of weekly average of daily [redacted] during the 14-week treatment period will be calculated for each subject as the date of having the first event - the first study drug dose date + 1 day. Subjects not having any event during the treatment period will have their time censored at the end of the treatment period. Time to onset of effect on [redacted] will be analyzed using the Cox proportional hazards model including treatment, randomization strata, and country as factors. The hazards ratio's 95% confidence interval and p-value will be reported. Kaplan-Meier curves will be provided. A sample of the SAS code is provided below:

```
proc phreg data=[redacted]
  class TRTP (ref='1') DISEASE_INDEX (ref='1')BIOLOGIC_EXPERIENCE (ref='1');
  model aval*cnsr(1) = DISEASE_INDEX BIOLOGIC_EXPERIENCE TRTP /
ties=exact rl;
```

```
  strata COUNTRY;
run;
quit;
```

Where TRTP = planned treatment group in numeric (1 = placebo, 2 = lirentelimab SC); DISEASE_INDEX = baseline disease severity index [1 = moderate (IGA=3) and 2 = severe (IGA=4)]; BIOLOGIC_EXPERIENCE = prior exposure to biologics [1 = biologic-naïve and 2 = biologic-exposed).

6.10.3 [redacted] Responder Rate

The endpoint will be analyzed using the same approaches as used for the analysis of the primary endpoint. A [redacted] responder is a subject who had at least a [redacted] reduction in score between the visit and baseline. A [redacted] responder is similarly defined.

6.10.4 Percent and Change from Baseline in [redacted]

These endpoints will be analyzed using the same approaches as that are used for the analysis of the secondary efficacy continuous endpoint of percent change in EASI.

The model will include fixed effects for baseline value, disease severity index, biologic-naïve vs biologic-exposed, country, treatment, study week, the treatment-by-week interaction, and the baseline by-week interaction and allow for random subject effects. Treatment and week will each be fitted as categorical variables. The model will assume unstructured covariance structure. If the model with unstructured covariance does not converge, then other covariance structures will be considered to model the within-subject errors. The Kenward-Rogers approach for computing denominator degrees of freedom will be used to account appropriately for pooling of within-subject and between-subject variance estimates. Data on subjects who prematurely discontinue the randomized treatment or initiate any treatment adjustments (e.g., use of prohibited/rescue medication) will be set to missing at the designated time points after withdrawal or after the start of such treatment changes. If fewer than 4 days of data are recorded within a particular week, the data for that week will be considered insufficient and the data will be set to missing for that week. Missing data entries in the eDiary and data set to missing as illustrated above will not be imputed.

6.10.5 Change from Baseline in [redacted]

The endpoint will be analyzed using the same approaches as that are used for the analysis of the secondary efficacy continuous endpoint of percent change in EASI.

6.10.6 Change from Baseline in [redacted]

The endpoint will be analyzed using the same approaches as that are used for the analysis of the secondary efficacy continuous endpoint of percent change in EASI.

6.10.7 Change from Baseline in [redacted]

The endpoint will be analyzed using the same approaches as that are used for the analysis of the secondary efficacy continuous endpoint of percent change in EASI.

6.10.8 Proportion of Subjects who Achieve Improvement from Baseline in [redacted]

Two endpoints will be considered; namely [redacted], and [redacted]
The endpoints will be analyzed using the same approaches as that are used for the analysis of the primary endpoint.

6.10.9 Change from baseline in percent [redacted]

The endpoint will be analyzed using the same approaches as that are used for the analysis of the secondary efficacy continuous endpoint of percent change in EASI.

6.10.10 Change from Baseline in [redacted]

The [redacted] is a [redacted] questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on [redacted]. The format is a simple response to [redacted], which assess [redacted] over the past week. The scoring of each question is defined in Table 3.

Table 3 [redacted] Scoring

Impact on [redacted]	Score
[redacted]	

The [redacted] is calculated by summing the score of each question resulting in a maximum of [redacted] and a minimum of [redacted] The higher the score, the more [redacted] (

Table 4, Table 5).

Table 4 Meaning of [redacted] Scores

Score	Meaning
[redacted]	

Table 5 [redacted] Details

Heading	Question	Maximum Score
[redacted]		

Interpretation of incorrectly completed questionnaires is as follows:

- If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of [redacted]
- If two or more questions are left unanswered the questionnaire is not scored
- If question 7 is answered 'yes' this is scored [redacted]
- If question 7 is answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this is then scored [redacted]
- If question 7 is answered 'no', but the second half is left incomplete, the score will remain 0.

The [redacted] will be analyzed by calculating the total score from its [redacted] displayed above via the methods outlined for the analysis of the secondary efficacy continuous endpoint of percent change in EASI.

6.11 Analysis of Pharmacokinetic Endpoint

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

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

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

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

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

6.12 Safety Analyses

6.12.1 Adverse Events

Safety assessments will be based mainly on the nature, frequency, relationship, and severity of adverse events (AE). The AE will be coded by primary System Organ Class (SOC) and Preferred Term (PT) according to MedDRA (version 21.0). The treatment-emergent adverse events (TEAE) will be summarized by the number and percentage (n and %) of subjects in each SOC and PT.

For summaries by relationship to study drug, “possibly related” will be combined with “related”, and “unlikely/remotely related” will be combined with “not related.” When multiple AE are reported with the same PT, the AE of the strongest relation to study drug will be included in the summary by relationship, and the AE of the most severe grade will be included in the summary by severity table.

The following AE incidence tables will be presented.

- Overview of TEAE to include
  - Number (%) of subjects who reported at least 1 TEAE

  - Number (%) of subjects who reported at least 1 treatment related TEAE
  - Number (%) of subjects who reported at least 1 severe TEAE
  - Number (%) of subjects who reported at least 1 serious TEAE
  - Number (%) of subjects who reported at least 1 TEAE leading to treatment discontinuation
  - Number (%) of subjects who reported at least 1 TEAE leading to study discontinuation
  - Number (%) of subjects who reported at least 1 TEAE of special interest (TEAESI)
- TEAE by PT sorted by decreasing order of subject incidence in the combined treatment group
- TEAE by SOC and PT in alphabetical order
- TEAE by SOC, PT, and maximum severity
- TEAE by SOC, PT, and strongest relationship to study drug
- TEAE leading to treatment discontinuation by SOC and PT, if warranted by sample size
- TEAE leading to study discontinuation by SOC and PT, if warranted by sample size
- Serious TEAE by SOC and PT, if warranted by sample size
- TEAESI by SOC and PT

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

Separate listings will be provided for TEAE leading to study discontinuation, TEAE of special interest, and treatment-emergent serious AE (TESAE).

6.12.2 Laboratory Test

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

Shift tables will be presented, in which, lab test results at baseline and post-baseline visit will be classified into below (<LLN), within (≥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 that the analysis window will be applied for the visits.

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

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

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

6.12.4 Electrocardiogram

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

6.12.5 Physical Examination

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

6.12.6 Analysis of Anti-Drug Antibodies

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

7. Validation

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

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

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

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

8. References

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

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

Mehta, C. R., & Pocock, S. J. (2011). Adaptive increase in sample size when interim results are promising: a practical guide with examples. Statistics in medicine, 30(28), 3267-3284.

9. Appendices

9.1 Appendix 1: Intercurrent Events and Definitions of Prohibited Medication Use and Rescue Medication/Treatment for AD Symptoms

9.2 Appendix 2: List of Tables, Figures, and Listings

9.1 Appendix 1: Intercurrent Events and Definitions of Prohibited Medication Use and Rescue Medication/Treatment for AD Symptoms

Intercurrent events (ICE) are considered to potentially confound the efficacy outcomes of the study and are defined as follows:

- Premature discontinuation from the double-blind portion of the study for any reason
- Use of prohibited medications during the study
- Use of rescue medication/therapy for symptoms of AD

Prohibited medications are defined as therapies that should not be taken during the course of the study either because of a potential impact on the assessment of efficacy and/or subject safety. Rescue medications/treatments are defined as any therapy or treatment taken during the course of the study for the specific purpose of alleviating AD symptoms that may have an impact on the assessment of efficacy and includes: (1) topical medications (including TCS, TCI and crisaborole), (2) systemic medications (including systemic corticosteroids, immunosuppressant, and biologics), and (3) treatments known to impact AD.

The following provides the details of the prohibited medications/therapies for this study:

1) Prohibited medications where route of administration includes topical/transdermal

   Topical Corticosteroids (TCS): ATC code D07
   High Potency TCS: ATC codes D07AC or D07AD
   Low or moderate potency TCS: ATC code D07, excluding D07AC or D07AD
   Topical calcineurin inhibitors (TCI): where Preferred Term includes tacrolimus, pimecrolimus
   Coal tar: ATC code D05AA
   Phosphodiesterase-4 Inhibitors (PDEi): ATC code L04AA32 where Preferred Term includes Crisaborole: ATC code D11AH, roflumilast (no topical ATC code) or apremilast gel

2) Prohibited systemic medications (including systemic corticosteroids, immunosuppressants, immunomodulators, and biologics)

   Systemic corticosteroids: ATC code is H02
   Immunosuppressants or immunomodulators: ATC code is L04
   Mycophenolate: ATC code is L04AA06
   Methotrexate: ATC code is L04AX
   Interferons: gamma: ATC code is L03AB where Preferred Terms include interferon gamma, interferonalfa-2b

Leukotriene inhibitors: ATC code is R03DC where Preferred Term includes Ibudilast, Montelukast, Pranlukast, and Zafirlukast
Oral calcineurin inhibitors: ATC code is L04AD where Preferred Term includes Ciclosporin, Cyclosporin, Tacforius, Tacrolimus, Voclosporin
IV immunoglobulins: ATC code is J06B
Doxepin: ATC code is N06AA
Janus Kinase inhibitors (JAKi): ATC code is L01EJ where Preferred Term includes Delgocitinib, Fedratinib, Pacritinib, Ruxolitinib and ATC code is D11AH with Preferred Term Abrocitinib
Phosphodiesterase-4 Inhibitors (PDEi): ATC code L04AA32 where Preferred Term includes apremilast (oral)
TNF inhibitors: ATC code is L04AB where Preferred Term includes Adalimumab, Afelimomab, Certolizumab, Etanercept, Golimumab, Infliximab, Opinercept, Ozoralizumab

Note 1: The use of a short course of systemic corticosteroids for a medical condition other than atopic dermatitis, in the event of medical necessity when no alternative non-steroid treatment is available, will be allowed provided that the use is limited to less than 5 days and the therapy is not taken within 28 days of the Day 99 visit.

Note 2: Leukotriene inhibitors: ATC code is R03DC where Preferred Term includes Ibudilast, Montelukast, Pranlukast, and Zafirlukast are permitted during the study provided that doses remain stable throughout the study unless change is required for an unforeseen medical necessity. Initiation of any new leukotriene inhibitor is prohibited.

Biologics:
Agents For Dermatitis, Excluding Corticosteroids: ATC code is D11A where preferred terms include Dupilumab, Tralokinumab
CD20 inhibitors: ATC code is L01F where preferred terms include Obinutuzumab, Ofatumumab
Selective Immunosuppressants: ATC code is L04AA where preferred terms include Abatacept, Abetimus, Alemtuzumab, Anifrolumab, Apremilast, Baricitinib, Begelomab, Belatacept, Belimumab, Belumosudil, Deucravacitinib, Eculizumab, Efalizumab, Emapalumab, Filgotinib, Fingolimod, Inebilizumab, Itacitinib, Natalizumab, Ocrelizumab, Ofatumumab, Ozanimod, Peficitinib, Pegcetacoplan, Ponesimod, Ravulizumab, Sutimlimab, Teprotumumab, Teriflunomide, Tofacitinib, Upadacitinib, Vedolizumab
Interleukin Inhibitors: ATC code is L04AC where preferred terms include Anakinra, Basiliximab, Bimekizumab, Briakinumab, Brodalumab, Canakinumab, Daclizumab, Guselkumab, Ixekizumab, Netakimab, Olokizumab, Rilonacept, Risankizumab, Sarilumab, Satralizumab, Secukinumab, Siltuximab, Sirukumab, Spesolimab, Tildrakizumab, Tocilizumab, Ustekinumab
Unspecified Immunosuppressants: No ATC code with Preferred Term including Barzolvolimab, Fezakinumab, Fletikumab, Gevokizumab, Gusacitinib, Ladarixin,

Lebrikizumab, Ligelizumab, Mirikizumab, Nemolizumab, Olamkicept, Tabalumab, Tregalizumab
Other Systemic Drugs for Airway Disease: ATC code R03D with Preferred Term including Benralizumab, Mepolizumab, Omalizumab, Reslizumab, Roflumilast, Tezepelumab and ATC code is R03DX with Preferred Term including Rituximab

3) The use of prescription emollients or emollients containing additives such as ceramide, hyaluronic acid, urea, or filaggrin are not allowed during the course of the study except as rescue therapy.

4) Treatments for Atopic Dermatitis:

The use of ultraviolet A or B (UVA or UVB), psoralen + UVA (PUVA), other phototherapy, or tanning beds is also not permitted during the study. The use of a tanning bed will not be considered rescue therapy.

9.2 Appendix 2: List of Tables, Figures, and Listings

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