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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Clinical Research Protocol AK002-018

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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Approval: [redacted]

08-Sep-2023 | 06:18 PDT

[redacted], MD, [redacted] Date

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Investigator Protocol Agreement

I have read the protocol specified below. In my formal capacity as Principal Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Allakos Inc. with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted Good Clinical Practice (GCP) principles, the Declaration of Helsinki in the applicable version, and the applicable legal and regulatory requirements, as well as to abide by the terms of this protocol.

Protocol Number: AK002-018

IND Number: 157566

NCT Number: NCT05155085

EudraCT Number: 2022-001625-79

Protocol Title: 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

Protocol Amendment 6: **08 September 2023**

Investigator Printed Name: _____

Investigator Signature: _____

Date: _____

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List of Abbreviations

AC	Allergic conjunctivitis
ACS	Allergic Conjunctivitis Symptom(s)
AD	Atopic dermatitis
ADA	Anti-drug-antibody
ADCC	Antibody-dependent cellular cytotoxicity
ADL	Activities of daily living
AE	Adverse event(s)
AESI	Adverse event(s) of special interest
AKC	Atopic keratoconjunctivitis
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
anti-HBc	Antibody to Hepatitis B core antigen
Anti-HCV	Hepatitis C virus antibody
AST	Aspartate aminotransferase
[redacted]	[redacted]
CBC	Complete blood count
CFR	Code of Federal Regulation
CI	Confidence interval
cm	Centimeter
COVID-19	Coronavirus disease 2019
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trials Facilitation and Coordination Group
CU	Chronic urticaria
[redacted]	[redacted]
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EG	Eosinophilic gastritis
ELISA	Enzyme-linked immunosorbent assay
EoD	Eosinophilic duodenitis (formerly referred to as eosinophilic gastroenteritis)
EOS	End of study

ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation (European Union)
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council on Harmonisation
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IGA	Investigator Global Assessment
IgE	Immunoglobulin E
IgG1	Immunoglobulin G1
IND	Investigational New Drug (application)
IP	Investigational product
IRB	Institutional Review Board
IRR	Infusion-related reaction (for intravenous infusion) Injection-related reaction (for subcutaneous injection)
IRT	Interactive Response Technology (system)
ISM	Indolent systemic mastocytosis
ITIM	Immunoreceptor tyrosine-based inhibitory motif
ITT	Intent to treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
JAK	Janus kinase(s)
kg	Kilogram
LARC	Long-Acting Reversible Contraceptives

LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intention-to-Treat
mIU	Milli-international units
mL	Milliliter
mM	Millimolar
MMRM	Mixed model for repeated measures
mTOR	mammalian Target of Rapamycin
NCI	National Cancer Institute
NCS	Not clinically significant
NOAEL	No-observed-adverse-effect level
NOEL	No-observed effect level
NRS	Numeric Rating Scale
OSS	Ocular Signs and Symptoms
PD	Pharmacodynamics
PDE4	Phosphodiesterase-4
PEF	Peak expiratory flow
PID	Patient identification number
PK	Pharmacokinetic(s)
PP	Per Protocol
[redacted]	[redacted]
PRO	Patient reported outcome
PUVA	Psoralen + ultraviolet A or B (UVA or UVB)
QoL	Quality of Life
SAE	Serious adverse event(s)
SAP	Statistical Analysis Plan
SC	Subcutaneous
[redacted]	[redacted]
Siglec	Sialic acid-binding, immunoglobulin-like lectin
SOC	System organ class
TEAE	Treatment-emergent adverse event(s)
TEAESI	Treatment-emergent adverse event(s) of special interest

TNF	Tumor necrosis factor
µL	Microliter
ULN	Upper limit of normal
USP	United States Pharmacopeia
UVA	Ultraviolet A
UVB	Ultraviolet B
[redacted]	[redacted]
vIGA	Validated Investigator Global Assessment
VKC	Vernal conjunctivitis
w/v	Weight/Volume
WOCBP	Women of childbearing potential

1. Protocol Synopsis

Title:	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
Sponsor:	Allakos Inc.
Number of Sites:	Up to 70 sites in the United States and Germany
Number of Subjects:	Approximately 130

Nonclinical Background

Lirentelimab is a humanized non-fucosylated immunoglobulin G1 (IgG1) monoclonal antibody directed against Siglec-8, a member of the CD33-related family of sialic acid-binding, immunoglobulin-like lectins (Siglecs). Siglec-8 has a restricted tissue distribution, expressed selectively on the surface of mature eosinophils and mast cells, but not in early precursors of these cell populations. In blood, binding of lirentelimab to Siglec-8 induces antibody-dependent cellular cytotoxicity (ADCC) against eosinophils, leading to rapid and sustained depletion of these cells from the circulation. In the tissue, lirentelimab induces direct apoptosis of eosinophils and inhibition of mast cells.

Lirentelimab has been produced in 2 formulations: 1 for intravenous infusion (lirentelimab IV) and 1 for subcutaneous injection (lirentelimab SC) (see Test Product, Dose, and Administration).

Clinical Background

Lirentelimab IV, administered every 4 weeks, has been previously tested in over 700 healthy volunteers and patients with indolent systemic mastocytosis (ISM), chronic urticaria (CU), severe allergic conjunctivitis (AC), mast cell gastritis, and eosinophilic gastritis (EG) and/or eosinophilic duodenitis (EoD). Multiple doses of 3 mg/kg have been given to patients with ISM, CU, AC, mast cell gastritis, and EG and/or EoD.

In general, lirentelimab IV has been well tolerated. The most common treatment-emergent adverse events (TEAE) observed were infusion-related reactions (IRR). The IRR were mostly mild to moderate and occurred most often during the first infusion. IRR that were deemed more serious typically resolved within 24 hours, and additional corticosteroids and/or antihistamines were used in cases when slowing the rate of infusion and additional supportive care alone did not resolve the issue. Common symptoms of IRR were headache, nausea, sweating, flushing, and redness. Most IRR that occurred during the infusion could be managed by slowing or temporary interruption of the infusion, with minimal intervention. The risk of IRR has been substantially reduced by administration of a single dose of oral corticosteroid (e.g., prednisone 60 mg) given orally 12 to 24 hours prior to the first dose of lirentelimab IV.

Study AK002-017 evaluated the pharmacokinetics (PK) and pharmacodynamics (PD) of lirentelimab IV and SC in healthy volunteers. Subjects received 0.3, 1, 3, or 5 mg/kg or a fixed dose of 300 mg or 450 mg lirentelimab SC, or 1 mg/kg or 3 mg/kg lirentelimab IV.

Clinical Background cont.

In each of the SC cohorts, 8 subjects were randomized to lirentelimab (6 per group) or placebo (2 per group) in a double-blind manner; 12 subjects received lirentelimab IV (6 subjects per group) in an open-label manner.

The study showed that the PD effect (depletion of blood eosinophils) occurred within 1 hour of dosing and lasted for at least 1 month at IV and SC doses of 1 mg/kg and for 3 months at all higher IV and SC doses. The SC injections were well tolerated, and no injection site reactions or general injection reactions were noted at any dose demonstrating suitability for further evaluation.

In Study AK002-005 in patients with severe AC, lirentelimab demonstrated clinical activity in relieving the signs and symptoms of severe AC across all measured domains. The study showed a 61% improvement in patient-reported ocular symptoms (total allergic conjunctivitis symptoms [ACS]) and 79% of subjects were deemed responders at 2 weeks following the final lirentelimab dose compared to baseline. Investigator-assessed ocular signs and symptoms (total OSS) also improved by 53%, and 83% of subjects were deemed responders at the final dose time point compared to baseline. Additionally, symptom burden was assessed across multiple atopic comorbidities, and symptom severity decreased substantially across all conditions assessed, including in atopic dermatitis (AD), asthma, and rhinitis.

The lack of treatment-related adverse events (AE) beyond IRR in the IV studies combined with the clinical activity observed in treating multiple allergic conditions and the return of signs and symptoms off treatment make lirentelimab a potentially promising candidate for multiple eosinophil and mast cell-driven inflammatory diseases, including AD.

Target Disease Background and Rationale for the Study

Atopic dermatitis 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 pathogenesis of AD is complex and involves abnormalities in skin barrier function, altered skin flora, and immune dysregulation (Fuxench, 2019). There is increased expression of Th2 and Th22 cytokines like IL-4, IL-13, IL-31, and IL-22. Mast cell numbers are elevated in the skin of AD patients. These cells, by virtue of producing pruritogenic mediators like histamine, tryptase and IL-31, might contribute to AD symptoms. In addition, mast cells may contribute to neurogenic inflammation by interacting with sensory nerves. In addition to mast cells, eosinophils may be elevated in patients with AD. It has been demonstrated that eosinophils taken from AD biopsies are activated and show delayed programmed cell death. Taken together, these findings suggest that activation and degranulation of mast cells and eosinophils may be a major component in the pathogenesis of AD and may represent suitable targets for therapeutic intervention.

Atopic dermatitis patients typically experience dry skin and intense pruritus, which can lead to development of erythematous papules with exudation, crusting, and excoriation. A recent study of adults with moderate-to-severe AD found that 70.5% reported severe, unbearable itch in the past 2 weeks, 85.8% reported daily itch, and 62.8% reported itching at least 12 hours per day. Chronically, this often leads to skin thickening and lichenification, most commonly in skin flexures.

Target Disease Background and Rationale for the Study cont.

Atopic dermatitis may involve the face, neck, trunk, and extremities. Atopic dermatitis follows a chronic relapsing course and can be complicated by development of bacterial and viral skin infections. Patients with AD also have an increased risk of allergic rhinitis, asthma, food allergies, and ocular conditions like atopic keratoconjunctivitis (AKC) and vernal conjunctivitis (VKC).

The main goals of AD treatment are to maintain adequate skin hydration, reduce pruritus, and prevent exacerbations. While oral anti-histaminic agents may help reduce pruritus, topical agents are the mainstay of treatment. These include moisturizing/emollient preparations, which protect the skin barrier and prevent water loss. Along with moisturizing agents, topical anti-inflammatory agents such as corticosteroids and calcineurin inhibitors (e.g., tacrolimus and pimecrolimus) are used for mild-to-moderate disease as second line options. Crisaborole, a topical phosphodiesterase 4 (PDE4) inhibitor, was approved by the FDA in December 2016, and is used for treatment of mild-to-moderate AD.

While topical agents can be effective in mild-to-moderate disease, there are long term safety concerns. Topical steroids can cause skin atrophy and possible adrenal suppression due to systemic absorption. Tacrolimus and pimecrolimus carry a potential risk of skin cancer, which has resulted in a black box warning by the FDA.

The management of moderate-to-severe disease is more difficult. Patients can be treated with phototherapy (3 times per week), which is cumbersome, expensive, and may increase the risk of developing skin cancer. Oral corticosteroids are occasionally used but are limited by side effects including increased risk of diabetes, hypertension, adrenal suppression, and eye diseases like glaucoma and cataracts. An oral calcineurin inhibitor (cyclosporin) can be used but requires frequent monitoring of drug levels and carries risks of hypertension, nephrotoxicity, hypertrichosis, and gum hyperplasia. Also, long-term use of steroids and cyclosporin leads to immunosuppression and increased risk of infections.

In March 2017, the FDA approved dupilumab for the treatment of adult patients with moderate-to-severe AD not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab is a fully human monoclonal antibody that binds to the alpha subunit of the IL-4 receptor and inhibits signaling of IL-4 and IL-13, altering T-cell mediated immune response, which is believed to play a role in AD. The long-term (52 week) safety and efficacy of dupilumab was evaluated in a randomized, double-blind, placebo-controlled study. Concomitant use of topical corticosteroids (and topical calcineurin inhibitors, if indicated) was allowed.

In the dupilumab study, at Week 52, more patients in the dupilumab-treated group achieved the Investigator Global Assessment (IGA) and Eczema Area and Severity Index (EASI)-75 endpoints than the placebo-treated group (approximately 40% versus 13% and 65% versus 22%, respectively). However, the dupilumab-treated patients had a 2-fold higher incidence of eye disorders including non-infectious conjunctivitis. There continues to be a substantial need for new and better treatments for moderate-to-severe AD. By reducing eosinophil numbers and blocking mast cell activation, lirentelimab may be useful in the treatment of patients with AD.

Target Disease Background and Rationale for the Study cont.

This proof-of-concept study will evaluate the safety, tolerability, and PD of repeat doses of lirentelimab SC in patients with moderate-to-severe AD and provide evidence for efficacy as assessed by symptomatology and skin examination. In this study, subjects with moderate-to-severe disease, which is defined using the following criteria, will be included:

- Chronic AD that has been diagnosed and present for at least 3 years at the time of screening.
- Subjects who have failed to respond to medicated topical treatments (corticosteroids, calcineurin inhibitors and/or crisaborole) or when these treatments are contraindicated or not medically advisable for the subject.
- At the screening visit, the subject must have an EASI score of ≥16, involvement of ≥10% of body surface area (BSA), and an IGA score of ≥3.

These well-established measures will objectively define the severity of the disease at the time of entry into the study.

Rationale for Dose Selection

A dosing regimen of 300 mg lirentelimab SC administered every 2 weeks for 7 doses is proposed. This regimen is based on PK modeling for Study AK002-017, comparing dosing regimens for the IV infusions vs. the SC injection doses administered every 28 days. These simulations showed that a dose of 300 mg lirentelimab SC provided a substantially lower C_{max} and slightly lower 1-month trough level than 3 mg/kg lirentelimab IV.

Discussion with experts participating in dermatologic trials with biologics and reports of external data from other compounds targeting AD support the use of higher or more frequent dosing than in other allergic diseases. Several studies have reported that higher or more frequent dosing is required for type II immune conditions, e.g., asthma, compared with AD. Dose-response relationships and results across multiple endpoints show trends toward improved efficacy with increasing dose and duration and suggest that further increases in dose or treatment duration might improve efficacy (Castro, 2018; Corren, 2017; Silverberg, 2020; Simpson, 2018; Simpson, 2019; Simpson, 2020; Wollenberg, 2019). Consequently, increasing the dose frequency of the 300 mg dose from every 4 weeks to every 2 weeks is proposed for the AK002-018 study.

Simulations using AK002-017 study data indicate that a fixed dose of lirentelimab SC 300 mg every 2 weeks is expected to provide greater exposure than the 300 mg dose administered monthly without an increased C_{max} compared with the 3 mg/kg IV dose. This dose and frequency of administration will result in higher steady state levels and is supported by the available safety and tolerability profile of lirentelimab in patients with other eosinophilic and mast cell diseases.

Sample Size

Approximately 130 evaluable adult subjects with moderate-to-severe AD inadequately controlled by topical treatments will be enrolled. 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.

Sample Size cont.

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.

Study Design

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 up to 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 considered to be competitive. To ensure the enrollment goal is achieved in a timely manner, up to 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 in order 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, [redacted] 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

Study Design cont.

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 (see Section 8.5 Exclusion Criteria) 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, 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.

Primary Objective and Endpoint

The primary objective of the study will be to characterize the efficacy of lirentelimab SC in adult subjects with AD as assessed by the difference in the proportion of subjects who achieve EASI-75 at Week 14.

Secondary Objectives and Endpoints

To further characterize the efficacy of lirentelimab SC in adult subjects with AD as measured by the following:

- % Change in EASI from baseline to Week 14.

Secondary Objectives and Endpoints cont.

- Proportion of subjects with IGA of 0 or 1 and a 2-point improvement at Week 14 compared with baseline.

Exploratory Objectives and Endpoints

The exploratory objectives of the study are to better characterize the timing and nature of the clinical response to lirentelimab SC in adult subjects as measured by the following exploratory efficacy endpoints:

- 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].
- 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 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]

Safety Objectives

To evaluate the safety and tolerability of lirentelimab SC in subjects with AD by determining AE incidence and severity, study withdrawals due to AE, changes in vital signs and laboratory tests including immunogenicity, changes in concomitant medication use due to AE, and other safety parameters.

Subject Selection Criteria

Inclusion Criteria: Subjects are eligible for the study if all of the following criteria are met:

1) Subject is able to understand the information on the study, has the capacity to consent, and has provided written informed consent.

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

Subject Selection Criteria – Inclusion Criteria cont.

3) Chronic AD (as defined by the American Academy of Dermatology Consensus Criteria) (Eichenfield, 2014) that has been present for at least 3 years before screening visit.

4) Documented recent history of inadequate response to treatment with topical medications such as topical corticosteroids, calcineurin inhibitors, JAK inhibitors, or PDE4 inhibitors (crisaborole) for at least 4 weeks in the 6 months prior to screening, or subjects for whom these topical treatments are otherwise medically inadvisable (e.g., because of side effects or safety risks).

5) Subject who are biologic-naïve or biologic-exposed. Biologic-exposed includes subjects who have demonstrated secondary loss of response, intolerance, or lack of access to biologics due to economic reasons.

6) EASI score of ≥16 at screening and at baseline.

7) Involvement of at least 10% or more of BSA at screening and at baseline.

8) An IGA score of 3 or above on a scale from 0–4 at screening and at baseline.

9) The subject should have applied a stable dose of non-medicated, non-prescription, topical emollient at least twice daily for 7 consecutive days immediately before the baseline visit.

10) Willing to apply a stable dose of non-medicated, non-prescription, topical emollient, as recommended by the Investigator at least twice daily for the duration of the study, if not already on an emollient at the time of screening.

11) Commitment to remain on the same dose(s) of AD medication(s), including topical emollients, for the entire duration of study participation unless dose modification is due to unforeseen medical necessity.

12) Willing and able to comply with the study procedures and visit schedule including follow-up visits.

13) Female subjects must be either postmenopausal (defined as no menses for 12 months without an alternative medical cause) with FSH level >30 mIU/mL at screening or surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months, or if of childbearing potential, have a negative serum pregnancy test and agree to use a highly effective method of contraception as defined in this protocol or abstain from sexual activity, if compliant with preferred and usual lifestyle of the subject, from screening until the end of the study or for 120 days following the last dose of study drug, whichever is longer.

    In the case of a postmenopausal female subject with FSH level ≤30 mIU/mL at screening, the subject will be required to have a negative serum pregnancy test during the screening period and will also be required to have a negative urine dipstick pregnancy test prior to dosing and at each study visit.

14) Male subjects with female partners of childbearing potential must agree to use a highly effective method of contraception as defined in this protocol or abstain from sexual activity from screening until the end of the study or for 120 days following the last dose of study drug, whichever is longer.

All fertile men with female partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

Exclusion Criteria: Subjects will be excluded from the study if they meet any of the following criteria:

1) Current use of biologics for any indication.

2) Demonstrated lack of primary response to treatment with a biologic for the treatment of AD defined as no response to treatment despite complete adherence to the prescribed regimen for at least 3 months (primary non-responders).

3) Use of any of the following treatments within 4 weeks prior to the baseline visit or any condition that in the opinion of the Investigator is likely to require such treatment(s) during the first 4 weeks of study treatment:
   - Phototherapy for AD
   - Immunosuppressive or immunomodulatory drugs, including but not limited to systemic calcineurin inhibitors (e.g., cyclosporin, tacrolimus), mTOR inhibitors (e.g., sirolimus, everolimus), anti-metabolites (e.g., azathioprine, methotrexate, 6-mercaptopurine, leflunomide, mycophenolate mofetil), alkylating agents (e.g., cyclophosphamide), eosinophil-depleting drugs (e.g., pramipexole), and systemic corticosteroids
   - Oral JAK inhibitors within 8 weeks of baseline visit (requires discussion with Allakos Medical Monitor prior to subject enrolling in study)

4) Treatment with biologics:
   - Any cell-depleting agents including but not limited to rituximab within 6 months prior to the baseline visit or until lymphocyte count returns to normal, whichever is longer
   - TNF inhibitors (e.g., infliximab, adalimumab) and other biologics (e.g., dupilumab, omalizumab, etc.) within 5 half-lives, if known, or 8 weeks prior to the baseline visit, whichever is longer

5) Any use of topical corticosteroids, topical calcineurin inhibitors, topical JAK inhibitors (e.g., ruxolitinib), or topical PDE4 inhibitors (crisaborole) for the treatment of AD within 1 week prior to the baseline visit.

6) Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit.

7) Treatment with chemotherapy or radiotherapy in the preceding 6 months.

8) Presence of skin comorbidities/concomitant conditions that may interfere with study assessments or interpretation of study results.

9) Planned or anticipated use of any prohibited medication.

10) History of malignancy except carcinoma in situ in the cervix, early-stage prostate cancer, or non-melanoma skin cancers.

Subject Selection Criteria – Exclusion Criteria cont.

11) Any disease, condition (medical or surgical), or cardiac abnormality that in the opinion of the Investigator would place the subject at increased risk.

12) A helminth parasitic infection diagnosed within 6 months prior to the date informed consent is obtained that has not been treated with or has failed to respond to standard-of-care therapy.

13) Evidence of active hepatitis B or C at screening based on serology.

14) Evidence of active HIV infection at screening based on serology.

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

16) Presence of an abnormal screening laboratory value considered to be clinically significant by the Investigator.

17) Known or suspected history of alcohol, drug, or other substance abuse or dependence that in the opinion of the Investigator may interfere with study participation or assessments.

18) Prior exposure to lirentelimab or known hypersensitivity to any constituent of the study drug.

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

20) Subjects who weigh <40 kg at screening.

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

22) Vaccination with live attenuated vaccines within 30 days prior to initiation of treatment in the study, during the treatment period, or vaccination expected within 5 half-lives (4 months) of study drug administration.

    Note: This exclusion criterion does not apply to all types and formulations of vaccines (including live attenuated vaccines) currently authorized/approved by FDA or other regulatory authority for the prevention of COVID-19, which may be administered before, during, or after the study.

    The vaccine should not be administered within 3 days before and within 3 days after the administration of lirentelimab so that any side effects caused by either of the 2 medications can be more easily determined.

23) Employees or relatives of the Sponsor or the Investigator, or other persons dependent on the Sponsor or the Investigator.

24) Commitment to an institution by order issued either by the judicial or the administrative authorities.

Subject Selection Criteria – Exclusion Criteria cont.

25) Presence of a SARS-CoV-2 infection and/or have not completed an authorized/approved COVID-19 primary immunization series as per national recommendations at the time of screening. (Germany only)

Acceptable and required documentation to confirm inclusion and exclusion criteria will be further explained in the Study Reference Manual and listed in the eCRF.

Test Product, Dose, and Administration

Lirentelimab SC Drug Product: The lirentelimab drug product is supplied in 2R Type I clear glass vials, securely sealed with a fluoropolymer-coated bromobutyl stopper and aluminum flip-off cap. It is intended for subcutaneous injection. Each drug product vial contains a nominal volume of 1 mL. It is a sterile, preservative-free solution that contains [redacted], pH 6.0 in Water for Injection (WFI). The solution is visually characterized as clear to slightly opalescent, appearing colorless to slightly yellow.

Placebo SC Product: The placebo is supplied in 2R Type I clear glass vials, securely sealed with a fluoropolymer-coated bromobutyl stopper and aluminum flip-off cap. It is intended for subcutaneous injection. Each placebo vial contains a nominal volume of 1 mL. It is a sterile, preservative-free solution that contains [redacted], pH 6.0 in WFI. The solution is visually characterized as clear to slightly opalescent, appearing colorless to slightly yellow.

Dosing (lirentelimab SC or placebo SC) will comprise a single 2 mL SC injection administered in the front of the thigh with a 27-gauge SC needle.

A total of seven doses of lirentelimab SC or placebo SC will be administered biweekly over 12 weeks.

Lirentelimab SC or placebo SC (based on randomization assignment) will be administered on Day 1, Dose 1; Day 15 (±5), Dose 2; Day 29 (±5), Dose 3; Day 43 (±5), Dose 4; Day 57 (±5), Dose 5; Day 71 (±5), Dose 6; and Day 85 (±5), Dose 7.

Subjects will be observed for at least 1 hour after each injection.

Following the double-blind period of the study, subjects will be given the option of entering the OLE period of the study, contingent on meeting certain study criteria. Subjects will receive 7 doses of 300 mg lirentelimab SC during the OLE period.

Duration of Subject Study Participation

The total study duration for each subject in the double-blind period of the study will be approximately 7 months. If a subject chooses to enter the OLE period, the total study duration will be approximately 9 months, which includes:

- A screening period of approximately 2 weeks prior to study drug administration.

Duration of Subject Study Participation cont.

- A treatment period of 12 weeks (administration of lirentelimab SC or placebo SC every 2 weeks for 7 doses).
- An optional open-label period of 12 weeks (administration of lirentelimab SC every 2 weeks for 7 doses).
- A follow-up period of 12 weeks after the last dose of study drug in the OLE period. Subjects who do not enter the OLE period of the study will be followed for 12 weeks after the last dose in the double-blind period of the study.

Efficacy Evaluations

Primary Efficacy Endpoint: The primary efficacy endpoint in the study will be proportion of subjects who achieve EASI-75 at Week 14.

Secondary Efficacy Endpoints:

- % 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.

Exploratory Efficacy Endpoints:

- 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]
- 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 SC as 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]

Safety Evaluations

Safety and tolerability will be assessed throughout the study by monitoring and evaluating AE, including reactions to the SC injection. All TEAE will be collected from the start of study drug administration through Day 169 (±5 days) or Early Termination (ET).

Severity will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) tables and toxicity grading scale (version 5 or the current version). All AE will be assigned a severity grade and will be assessed to determine whether they are clinically significant and related to study drug.

Additional safety evaluations include clinical laboratory tests comprising anti-drug antibody (ADA) to lirentelimab SC, complete blood counts, chemistries, and urinalyses; physical exams; and vital sign measurements.

The Medical Monitor will review blinded safety data throughout the study.

Pharmacodynamic Evaluations

Absolute and percent eosinophil counts in peripheral blood will be collected.

Pharmacokinetic and Anti-Drug-Antibody Evaluations

Pharmacokinetic (PK) blood samples will be obtained prior to the first dose on Day 1 and predose (as applicable) on Days 8, 15, 29, 43, 57, 71, 85, 99, 141, and 169 or ET. Additional PK samples will be collected in the OLE period of the study.

Blood (serum) will be collected for assessment of lirentelimab ADA using a validated assay method. The ADA blood samples will be obtained predose on Days 1, 43, and 85, as well as on Days 8, 99, and 169, and in the event of a suspected immunogenicity-related AE.

Statistical Analysis

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.

Statistical Analysis cont.

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. 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.

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, 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 modified intent-to-treat (mITT) population, as well as per protocol (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.

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.

2. Background

2.1 Siglec-8 and Lirentelimab

Siglec-8, a member of the CD33-related family of sialic acid-binding, immunoglobulin-like lectins (Siglecs), is a transmembrane cell surface protein with restricted tissue distribution, expressed selectively on the surface of mature eosinophils and mast cells, but not in early precursors of these cell populations. Siglec-8 contains 3 extracellular immunoglobulin-like domains, a transmembrane region, and a cytoplasmic tail containing 2 tyrosine-based signaling motifs including an immunoreceptor tyrosine-based inhibitory motif (ITIM) with inhibitory function. Engagement of Siglec-8 in mast cells can result in inhibition of mediator release, and in eosinophils can induce apoptosis (Bochner, 2009). Lirentelimab also shows potent antibody-dependent cellular cytotoxicity (ADCC) against eosinophils in vivo and in vitro.

2.2 Overview of Nonclinical Studies

Lirentelimab is a humanized non-fucosylated immunoglobulin G1 (IgG1) monoclonal antibody directed against Siglec-8, a member of the CD33-related family of sialic acid-binding, immunoglobulin-like lectins (Siglecs). Siglec-8 has a restricted tissue distribution, expressed selectively on the surface of mature eosinophils and mast cells, but not in early precursors of these cell populations. In blood, binding of lirentelimab to Siglec-8 induces ADCC against eosinophils, leading to rapid and sustained depletion of these cells from the circulation. In the tissue, lirentelimab induces direct apoptosis of eosinophils and inhibition of mast cells.

Lirentelimab has been produced in 2 formulations: 1 for intravenous infusion (lirentelimab IV) and 1 for subcutaneous injection (lirentelimab SC) (see Section 10: Study Treatment).

Siglec-8 is not expressed in species other than humans and high-order primates, and therefore, 2 novel mouse models have been developed for in vivo testing of lirentelimab. Lirentelimab has been studied in Siglec-8 humanized and transgenic mouse models and with human blood and tissue cells. The first model uses immunodeficient mice capable of generating human immune cells including mast cells and eosinophils when engrafted with human hematopoietic stem cells. The ability of anti-Siglec-8 antibodies to inhibit mast cell-mediated reactions has been evaluated in this model. The second rodent model is a transgenic mouse line that expresses human Siglec-8. The expression of Siglec-8 on the cell surface in these mice is restricted to eosinophils, mast cells, and basophils, a pattern of surface expression equivalent to that in humans. Anti-Siglec-8 antibodies can prevent IgE-mediated anaphylaxis in this transgenic mouse line, indicating that Siglec-8 is pharmacologically active in the model. The ability of lirentelimab to affect mast cells and eosinophils has been evaluated in this model.

Lirentelimab inhibits IgE-mediated mast cell degranulation and release of the newly formed mediator prostaglandin D2 in vitro without affecting mast cell viability. In peripheral blood preparations from normal human donors, lirentelimab shows selective depletion of eosinophils. Importantly, in a whole-blood cytokine-release assay using immobilized lirentelimab to enhance the potential for antibody crosslinking, lirentelimab did not lead to dose-dependent release of pro-inflammatory cytokines.

To evaluate the in vivo activity of anti-Siglec-8 antibodies in an immunocompetent rodent model, a transgenic mouse strain has been developed that selectively expresses human Siglec-8 on the surface of mouse mast cells, eosinophils, and basophils. In single-dose and repeat-dose studies in Siglec-8 transgenic mice, lirentelimab demonstrated selective depletion of peritoneal mast cells and circulating and tissue (spleen) eosinophils and basophils.

In the 1-month and 6-month Good Laboratory Practice (GLP) toxicity and toxicokinetic studies, lirentelimab IV was well tolerated at doses of 50 mg/kg and 100 mg/kg, 5-fold and 10-fold, respectively, the level of the highest dose proposed to be studied in humans. Lirentelimab showed sustained systemic exposure in Siglec-8 transgenic mice with an extended terminal half-life estimated as 272 hours or 337 hours following single IV administration of 50 mg/kg or 100 mg/kg, respectively. There was no evidence of anti-drug antibodies (ADA) in either study. Decreases in eosinophil counts in both sexes were observed, which reflect the expected pharmacology of lirentelimab. The no-observed-adverse-effect-level (NOAEL) following intravenous administration of lirentelimab to transgenic mice was 100 mg/kg.

A GLP toxicology study was conducted to characterize the local tolerance and bioavailability of lirentelimab SC in transgenic mice to support human clinical studies. The dose, 60 mg/kg, was selected to represent a dose level 6-fold higher than the highest human dose level (10 mg/kg), to identify a NOAEL/no observed effect level (NOEL) and was representative of the IV lirentelimab doses previously studied (50 mg/kg and 100 mg/kg). There were no lirentelimab-related clinical observations following SC or IV administration, and there were no lirentelimab-related skin reactions noted following SC or IV administration.

A GLP study of lirentelimab SC was conducted using C57Bl/6 male breeder mice and F0 generation Siglec-8 transgenic female mice to evaluate the effects of 60 mg/kg lirentelimab SC on fertility, development, and perinatal/postnatal reproduction, including postnatal behavior/function. Observations were continued through sexual maturity of the F1 generation mice. There were no lirentelimab-related effects on fertility, development, or perinatal/postnatal reproduction, or on the postnatal behavioral assessments. Based on these results, the NOAEL of lirentelimab SC was considered to be 60 mg/kg.

2.3 Overview of Clinical Studies

Lirentelimab IV, administered every 4 weeks, has been previously tested in over 700 healthy volunteers and patients with indolent systemic mastocytosis (ISM), chronic urticaria (CU), severe allergic conjunctivitis (AC), mast cell gastritis, and eosinophilic gastritis (EG) and/or eosinophilic duodenitis (EoD). Multiple doses of 3 mg/kg have been given to patients with ISM, CU, AC, mast cell gastritis, and EG and/or EoD.

In general, lirentelimab IV has been well tolerated. The most common treatment-emergent adverse events (TEAE) observed were infusion-related reactions (IRR). The IRR were mostly mild to moderate, and occurred most often during the first infusion. IRR that were deemed more serious typically resolved within 24 hours, and additional corticosteroids and/or antihistamines were used in cases when slowing the rate of infusion and additional supportive care alone did not resolve the issue. Common symptoms of IRR were headache, nausea, sweating, flushing, and redness. Most IRR that occurred during the infusion could be managed by slowing or temporary interruption of the infusion, with minimal intervention. In subjects with ISM, CU, severe AC, and EG/EoD, fewer adverse events (AE) including IRR were reported during the second and subsequent infusions when compared to the first infusion. The risk of IRR has been substantially reduced by administration of a single dose of oral corticosteroid (e.g., prednisone 60 mg) given orally 12 to 24 hours prior to the first dose of lirentelimab IV.

Study AK002-017 evaluated the PK and PD of lirentelimab IV and SC in healthy volunteers. Subjects received 0.3, 1, 3, or 5 mg/kg or a fixed dose of 300 mg or 450 mg lirentelimab SC, or 1 mg/kg or 3 mg/kg lirentelimab IV.

In each of the SC cohorts, 8 subjects were randomized to lirentelimab (6 per group) or placebo (2 per group) in a double-blind manner; 12 subjects received lirentelimab IV (6 subjects per group) in an open-label manner.

The study showed that the PD effect (depletion of blood eosinophils) occurred within 1 hour of dosing and lasted for at least 1 month at IV and SC doses of 1 mg/kg and for 3 months at all higher IV and SC doses. The SC injections were well tolerated, and no injection site reactions or general injection reactions were noted at any dose demonstrating suitability for further evaluation.

In the AK002-005 study in patients with severe AC, lirentelimab demonstrated clinical activity in relieving the signs and symptoms of severe AC across all measured domains. The study showed a 61% improvement in patient-reported ocular symptoms (total allergic conjunctivitis symptoms [ACS]) and 79% of subjects were deemed responders at 2 weeks following the final

lirentelimab dose compared to baseline. Investigator-assessed ocular signs and symptoms (total OSS) also improved by 53%, and 83% of subjects were deemed responders at the final dose time point compared to baseline. Additionally, symptom burden was assessed across multiple atopic comorbidities, and symptom severity decreased substantially across all conditions assessed, including in atopic dermatitis (AD), asthma, and rhinitis.

The lack of treatment-related adverse events (AE) beyond IRR in the IV studies combined with the clinical activity observed in treating multiple allergic conditions and the return of signs and symptoms off treatment make lirentelimab a potentially promising candidate for multiple eosinophil and mast cell-driven inflammatory diseases, including AD.

2.4 Atopic Dermatitis and Rationale for the Study

Atopic dermatitis 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 pathogenesis of AD is complex and involves abnormalities in skin barrier function, altered skin flora, and immune dysregulation (Fuxench, 2019). There is increased expression of Th2 and Th22 cytokines like IL-4, IL-13, IL-31, and IL-22. Mast cell numbers are elevated in the skin of AD patients. These cells, by virtue of producing pruritogenic mediators like histamine, tryptase and IL-31, might contribute to AD symptoms. In addition, mast cells may contribute to neurogenic inflammation by interacting with sensory nerves. In addition to mast cells, eosinophils may be elevated in patients with AD. It has been demonstrated that eosinophils taken from AD biopsies are activated and show delayed programmed cell death. Taken together, these findings suggest that activation and degranulation of mast cells and eosinophils may be a major component in the pathogenesis of AD and may represent suitable targets for therapeutic intervention.

Atopic dermatitis patients typically experience dry skin and intense pruritus, which can lead to development of erythematous papules with exudation, crusting, and excoriation. A recent study of adults with moderate-to-severe AD found that 70.5% reported severe, unbearable itch in the past 2 weeks, 85.8% reported daily itch, and 62.8% reported itching at least 12 hours per day. Chronically, this often leads to skin thickening and lichenification, most commonly in skin flexures.

Atopic dermatitis may involve the face, neck, trunk, and extremities. Atopic dermatitis follows a chronic relapsing course and can be complicated by development of bacterial and viral skin infections. Patients with AD also have an increased risk of allergic rhinitis, asthma, food allergies, and ocular conditions like atopic keratoconjunctivitis (AKC) and vernal conjunctivitis (VKC).

The main goals of AD treatment are to maintain adequate skin hydration, reduce pruritus and prevent exacerbations. While oral anti-histaminic agents may help reduce pruritus, topical agents are the mainstay of treatment. These include moisturizing/ emollient preparations, which protect the skin barrier and prevent water loss. Along with moisturizing agents, topical anti-inflammatory agents such as corticosteroids and calcineurin inhibitors (e.g., tacrolimus and pimecrolimus) are used for mild-to-moderate disease as second line options. Crisaborole, a topical phosphodiesterase 4 (PDE4) inhibitor, was approved by the FDA in December 2016, and is used for treatment of mild-to-moderate AD. While topical agents can be effective in mild-to-moderate disease, there are long term safety concerns. Topical steroids can cause skin atrophy and possible adrenal suppression due to systemic absorption. Tacrolimus and pimecrolimus carry a potential risk of skin cancer, which has resulted in a black box warning by the FDA.

The management of moderate-to-severe disease is more difficult. Patients can be treated with phototherapy (3 times per week), which is cumbersome, expensive, and may increase the risk of developing skin cancer. Oral corticosteroids are occasionally used but are limited by side effects including increased risk of diabetes, hypertension, adrenal suppression, and eye diseases like glaucoma and cataracts. An oral calcineurin inhibitor (cyclosporin) can be used but requires frequent monitoring of drug levels and carries risks of hypertension, nephrotoxicity, hypertrichosis, and gum hyperplasia. Also, long-term use of steroids and cyclosporin leads to immunosuppression and increased risk of infections.

In March 2017, the FDA approved dupilumab for the treatment of adult patients with moderate-to-severe AD not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab is a fully human monoclonal antibody that binds to the alpha subunit of the IL-4 receptor and inhibits signaling of IL-4 and IL-13, altering T-cell mediated immune response, which is believed to play a role in AD. The long-term (52 week) safety and efficacy of dupilumab was evaluated in a randomized, double-blind, placebo-controlled study. Concomitant use of topical corticosteroids (and topical calcineurin inhibitors, if indicated) was allowed.

In the dupilumab study at Week 52, more patients in the dupilumab-treated group achieved the Investigator Global Assessment (IGA) and Eczema Area and Severity Index (EASI)-75 endpoints than the placebo-treated group (approximately 40% versus 13% and 65% versus 22%, respectively). However, the dupilumab-treated patients had a 2-fold higher incidence of eye disorders including non-infectious conjunctivitis. There continues to be a substantial need for new and better treatments for moderate-to-severe AD. By reducing eosinophil numbers and blocking mast cell activation, lirentelimab may be useful in the treatment of patients with AD.

This proof-of-concept study will evaluate the safety, tolerability, and PD of repeat doses of lirentelimab SC in patients with moderate-to-severe AD and provide evidence for efficacy as assessed by symptomatology and skin examination. In this study, subjects with moderate-to-severe disease, which is defined using the following criteria, will be included:

- Chronic AD that has been diagnosed and present for at least 3 years at the time of screening.
- Subjects who have failed to respond to medicated topical treatments (corticosteroids, calcineurin inhibitors and/or crisaborole) or when these treatments are contraindicated or not medically advisable for the subject.
- At the screening visit the subject must have an EASI score of ≥16, involvement of ≥10% of body surface area (BSA), and an IGA score of ≥3.

These well-established measures will objectively define the severity of the disease at the time of entry into the study.

3. Rationale for Dose Selection

A dosing regimen of 300 mg lirentelimab SC administered every 2 weeks for 7 doses is proposed. This regimen is based on PK modeling for Study AK002-017, comparing dosing regimens for the IV infusion doses vs. the SC injection doses administered every 28 days. These simulations showed that a dose of 300 mg lirentelimab SC provided a substantially lower C_{max} and slightly lower 1-month trough level than 3 mg/kg lirentelimab IV.

Discussion with experts participating in dermatologic trials with biologics and reports of external data from other compounds targeting AD support the use of higher or more frequent dosing than in other allergic diseases. Several studies have reported that higher or more frequent dosing is required for type II immune conditions, for example asthma, compared with AD. Dose-response relationships and results across multiple endpoints show trends toward improved efficacy with increasing dose and duration and suggest that further increases in dose or treatment duration might improve efficacy (Castro, 2018; Corren, 2017; Simpson, 2018; Simpson, 2019; Simpson, 2020; Silverberg, 2020; Wollenberg, 2019). Consequently, increasing the dose frequency of the 300 mg dose from every 4 weeks to every 2 weeks is proposed for the AK002-018 study.

Simulations using AK002-017 study data indicate that a fixed dose of lirentelimab SC 300 mg every 2 weeks is expected to provide greater exposure than the 300 mg dose administered monthly without an increased C_{max} compared with the 3 mg/kg IV dose. This dose and frequency

of administration will result in higher steady state levels and is supported by an excellent safety and tolerability profile of lirentelimab in patients with other eosinophilic and mast cell diseases.

The concentration of lirentelimab SC of 150 mg/mL is consistent with an injection volume of 2 mL for the 300 mg dose, which was well tolerated without injection site reactions in Study AK002-017. When proof of concept is established, other lirentelimab SC doses and schedules may be explored.

4. Study Objectives and Endpoints

4.1 Primary Objective and Endpoint

The primary objective of the study will be to characterize the efficacy of lirentelimab SC in adult subjects with AD as assessed by the difference in the proportion of subjects who achieve EASI-75 at Week 14.

4.2 Secondary Objectives and Endpoints

To further characterize the efficacy of lirentelimab SC in adult subjects with AD as measured by the following:

- % 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 vs baseline.

4.3 Exploratory Objectives and Endpoints

The exploratory objectives of the study are to better characterize the timing and nature of the clinical response to lirentelimab SC in adult subjects as measure by the following exploratory efficacy endpoints:

- Change in [redacted] of sleep loss 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]

- 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 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]

4.4 Safety Objectives

To evaluate the safety and tolerability of lirentelimab SC in subjects with AD by determining AE incidence and severity, study withdrawals due to AE, changes in vital signs and laboratory tests including immunogenicity, changes in concomitant medication use due to AE, and other safety parameters.

Safety and tolerability will be assessed throughout the study by monitoring and evaluating AE, including any reactions to the SC injection. All TEAE will be collected from the start of study drug administration through Day 169 (±5 days) or Early Termination (ET) during the double-blind period of the study.

Severity will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) tables and toxicity grading scale (version 5 or most current version). All AE will be assigned a severity grade and will be assessed to determine whether they are clinically significant and related to study drug.

Additional safety evaluations include clinical laboratory tests comprising anti-drug antibody (ADA) to lirentelimab SC, complete blood counts, chemistries, and urinalyses; physical exams; and vital sign measurements.

The Medical Monitor will review blinded safety data throughout the study. Certain safety data (post-treatment cell differentials) collected during the double-blind period of the study will not be provided to study sites or to the Sponsor as it may cause bias. The designated Safety Monitor

will review blinded safety data as well as post-treatment cell counts and will escalate to the Medical Monitor, as needed, in a manner that does not cause bias.

An independent Data Monitoring Committee (iDMC) has been convened and will meet in accordance with the iDMC charter.

5. Study Design

5.1 Study Overview

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 up to 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 considered to be competitive. To ensure the enrollment goal is achieved in a timely manner, up to 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 in order 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, [redacted] 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). To ensure there is sufficient patient-reported outcome (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.

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 (see Section 8.5 Exclusion Criteria) 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, followed by 6 additional 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, 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 patients predose and post-dose at selected US sites. Providing biopsies is optional, and subjects will sign a separate consent form for biopsy collection.

The study is designed as follows:

- A screening period of approximately 14 days with baseline evaluations for study eligibility.
- During the screening period, the EASI, [redacted] will be determined, and a baseline will be established.
- If subjects meet eligibility criteria, the Interactive Response Technology (IRT) system will assign subjects 1:1 to receive 7 doses of 300 mg lirentelimab SC or placebo SC. Subjects will be stratified based on biologic-naïve vs biologic-exposed status and IGA score at baseline.
- Eligible subjects will receive the first dose of lirentelimab SC or identical placebo on Day 1. If the study drug is well tolerated (no stopping rules being met), subjects will receive additional doses of lirentelimab SC or placebo SC on Days 15 (Dose 2), 29 (Dose 3), 43 (Dose 4), 57 (Dose 5), 71 (Dose 6), and 85 (Dose 7).
- Subjects will be given an option of entering the OLE period to receive 7 additional doses of open-label study drug.
- Subjects will be followed for 12 additional weeks or 84 days after last dose if ET, after the double period or the OLE period.
- Subjects will remain at the site for at least 1 hour of observation following the end of the SC injection.
- Subjects will complete a number of assessments and questionnaires, including daily ePRO, throughout the duration of the study.
- Total study duration is approximately 7 months for the double-blind period and 9 months if the subject chooses to enter the OLE period.

5.2 Schedule of Events and Study Diagram

The overall schedule of assessments and procedures is described in Table 1. The study diagram is presented in Figure 1.

Table 1 Study AK002-018 Schedule of Assessments: Double-Blind Period

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 (see details in 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.

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).

Table 1 Notes cont.

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.

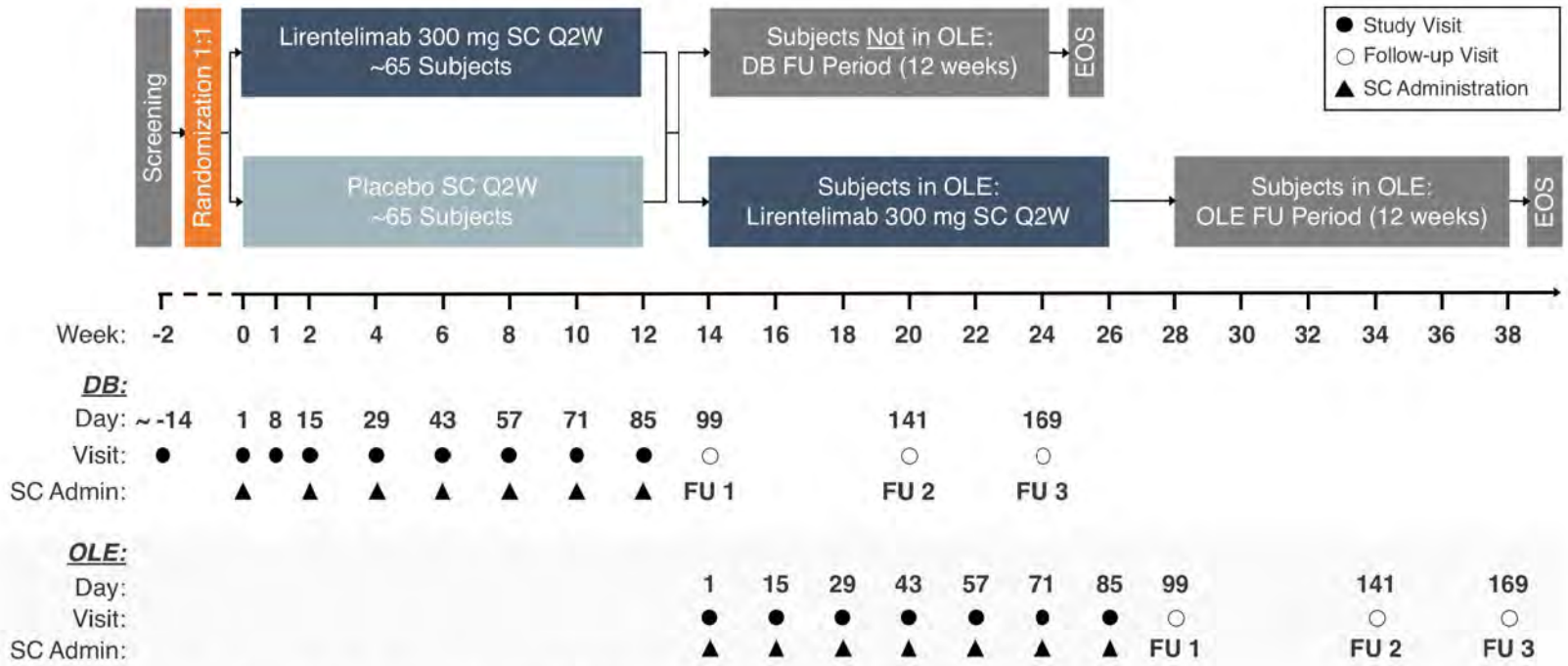
20) The capture of non-serious AE and adverse events of special interest (AESI) will begin after the first dose of study drug has occurred.

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.

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 and do not need to repeat Day 99 procedures if OLE Day 1 visit is completed on the same day as Day 99 visit.

Figure 1 Study Diagram



DB=Double-Blind Period; FU-Follow Up; SC=subcutaneous; OLE=Open Label Extension; EOS=End of Study

6. Estimand Considerations

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 after 14 weeks?"

Target of Estimation

Consistent with the ICH E9 Addendum (FDA, 2021), definition of the attributes of the estimand (target of estimation) is provided in this section.

The primary estimand of the study is a composite estimand, which estimates the effect of randomized treatment and accounts for non-responders based upon intercurrent events as defined.

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 as defined by the study inclusion criteria.

Variable (or Endpoint) to be Obtained for Each Subject that is Required to Address the Scientific Question

The primary endpoint to be obtained for each subject in this study to address the scientific question is the proportion of subjects who achieve EASI-75 at Week 14. For participants who drop out or initiate rescue or prohibited medication during the study, the outcome will be defined as "non-responder" after the date of such events.

Specification of How to Account for Intercurrent Events to Reflect the Scientific Question of Interest

The following intercurrent events will be anticipated and addressed:

- Premature discontinuation from the study
- Use of prohibited medications or rescue therapy during the study

For the analysis of the estimand, subjects who prematurely discontinue the randomized treatment or initiate any rescue or prohibited medication will be considered treatment non-responders at the designated time points after the start of such treatments.

7. Criteria for Evaluation

7.1 Safety Endpoints

The safety and tolerability of lirentelimab SC will be assessed by determining the incidence, relationship to study drug, and severity of TEAE, withdrawals due to AE, and changes in vital signs, laboratory tests, changes in concomitant medication use due to AE, immunogenicity, and other safety parameters. These endpoints will be based on the following:

- Adverse events (Section 14.1) including severity, withdrawals due to AE, and other safety parameters.
- Adverse events of special interest (AESI), injection-related reactions (IRR), malignancy, parasitic infections, and opportunistic infections (Section 14.3)
- Anti-drug antibodies (Section 12.3.6): Blood (serum) will be collected for assessment of ADA using a validated assay method.
- Blood chemistry (Section 12.3.1)
- Hematology (Section 12.3.1)
- Urinalysis (Section 12.3.4)
- Physical examination (Section 12.2.2 and Section 12.2.4)
- Changes in vital signs (Section 12.2.7)
- Changes in concomitant medication use due to AE (Section 12.2.1)

7.2 Pharmacokinetic Endpoints

Blood (serum) will be collected for assessment of lirentelimab SC concentrations using a validated enzyme-linked immunosorbent assay (ELISA) method.

The PK blood samples will be obtained predose on Day 1 (±3), Day 8 (±3), Days 15, 29, 43, 57, 71, and 85 (±5), and follow-up Days 99, 141, and 169 (14, 56, and 84 days [±5] after the last dose if ET). Additional PK samples will be collected in the OLE period of the study predose on all dosing days.

7.2.1 Primary Efficacy Endpoints

The primary efficacy endpoint in the study will be proportion of subjects who achieve EASI-75 at Week 14.

7.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will be the following:

- % 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 to placebo.

7.2.3 Exploratory Efficacy Endpoints

The following exploratory endpoints will be measured:

- 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]
- 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 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]

8. Subject Selection

8.1 Number of Subjects

A total of approximately 130 subjects with moderate-to-severe AD will be enrolled and randomized in a double-blind manner, 1:1, to receive 1 of the following treatments:

- Placebo SC administered every 2 weeks
- Lirentelimab SC at 300 mg administered every 2 weeks

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.

8.2 Number of Sites

Up to 70 sites in the United States and Germany will participate in this study.

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 considered to be competitive. To ensure the enrollment goal is achieved in a timely manner, up to 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 in order to meet the study timeline, then fewer sites may be needed.

8.3 Study Population

Approximately 130 male and female adult subjects with moderate-to-severe AD inadequately controlled by topical treatments will be enrolled in the study. Subjects will be either biologic-naïve or biologic-exposed. Biologic-exposed subjects include those who have demonstrated secondary loss of response, intolerance, or lack of access to biologics due to economic reasons.

8.4 Inclusion Criteria

Subjects are eligible for the study if all of the following criteria are met:

1) Subject is able to understand the information on the study, has the capacity to consent, and has provided written informed consent.
2) Male or female aged ≥18 and ≤80 years at the time of signing the ICF.

3) Chronic AD (as defined by the American Academy of Dermatology Consensus Criteria) (Eichenfield, 2014); that has been present for at least 3 years before screening visit.

4) Documented recent history of inadequate response to treatment with topical medications such as topical corticosteroids, calcineurin inhibitors, JAK inhibitors, or PDE4 inhibitors (crisaborole) for at least 4 weeks in the 6 months prior to screening, or subjects for whom these topical treatments are otherwise medically inadvisable (e.g., because of side effects or safety risks).

5) Subjects who are biologic-naïve or biologic-exposed. Biologic-exposed includes subjects who have demonstrated secondary loss of response, intolerance, or lack of access to biologics due to economic reasons.

6) EASI score of ≥16 at screening and at baseline.

7) Involvement of at least 10% or more of BSA at screening and at baseline.

8) An IGA score of 3 or above on a scale from 0–4 at screening and at baseline.

9) The subject should have applied a stable dose of non-medicated, non-prescription, topical emollient at least twice daily for 7 consecutive days immediately before the baseline visit.

10) Willing to apply a stable dose of non-medicated, non-prescription, topical emollient, as recommended by the Investigator at least twice daily for the duration of the study, if not already on an emollient at the time of screening.

11) Commitment to remain on the same dose(s) of AD medication(s), including topical emollients, for the entire duration of study participation unless dose modification is due to unforeseen medical necessity.

12) Willing and able to comply with the study procedures and visit schedule including follow-up visits.

13) Female subjects must be either postmenopausal (defined as no menses for 12 months without an alternative medical cause) with FSH level >30 mIU/mL at screening or surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months, or if of childbearing potential, have a negative serum pregnancy test and agree to use a highly effective method of contraception as defined in this protocol or abstain from sexual activity, if compliant with preferred and usual lifestyle of the subject, from screening until the end of the study or for 120 days following the last dose of study drug, whichever is longer.

In the case of a postmenopausal female subject with FSH level ≤30 mIU/mL at screening, the subject will be required to have a negative serum pregnancy test during the screening period and will also be required to have a negative urine dipstick pregnancy test prior to dosing and at each study visit.

14) Male subjects with female partners of childbearing potential must agree to use a highly effective method of contraception as defined in this protocol or abstain from sexual activity from screening until the end of the study or for 120 days following the last dose of study drug, whichever is longer. All fertile men with female partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

8.5 Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

1) Current use of biologics for any indication.

2) Demonstrated lack of primary response to treatment with a biologic for the treatment of AD defined as no response to treatment despite complete adherence to the prescribed regimen for at least 3 months (primary non-responders).

3) Use of any of the following treatments within 4 weeks prior to the baseline visit or any condition that in the opinion of the Investigator is likely to require such treatment(s) during the first 4 weeks of study treatment:

   - Phototherapy for AD
   - Immunosuppressive or immunomodulatory drugs, including but not limited to systemic calcineurin inhibitors (e.g., cyclosporin, tacrolimus), mTOR inhibitors (e.g., sirolimus, everolimus), anti-metabolites (e.g., azathioprine, methotrexate, 6-mercaptopurine, leflunomide, mycophenolate mofetil), alkylating agents (e.g., cyclophosphamide), eosinophil-depleting drugs (e.g., pramipexole), and systemic corticosteroids
   - Oral JAK inhibitors within 8 weeks of the baseline visit (requires discussion with Allakos Medical Monitor prior to subject enrolling in study)

4) Treatment with biologics:

   - Any cell-depleting agents including but not limited to rituximab; within 6 months prior to the baseline visit, or until lymphocyte count returns to normal, whichever is longer

- TNF inhibitors (e.g., infliximab, adalimumab) and other biologics (e.g., dupilumab, omalizumab, etc.) within 5 half-lives if known or 8 weeks prior to the baseline visit, whichever is longer

5) Any use of topical corticosteroids, topical calcineurin inhibitors, topical JAK inhibitors (e.g., ruxolitinib), or topical PDE4 inhibitors (crisaborole) for the treatment of AD within 1 week prior to the baseline visit.

6) Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit.

7) Treatment with chemotherapy or radiotherapy in the preceding 6 months.

8) Presence of skin comorbidities/concomitant conditions that may interfere with study assessments or interpretation of study results.

9) Planned or anticipated use of any prohibited medication.

10) History of malignancy except carcinoma in situ in the cervix, early stage prostate cancer, or non-melanoma skin cancers.

11) Any disease, condition (medical or surgical), or cardiac abnormality that in the opinion of the Investigator would place the subject at increased risk.

12) A helminth parasitic infection diagnosed within 6 months prior to the date informed consent is obtained that has not been treated with or has failed to respond to standard-of-care therapy.

13) Evidence of active hepatitis B or C at screening based on serology.

14) Evidence of active HIV infection at screening based on serology.

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

16) Presence of an abnormal screening laboratory value considered to be clinically significant by the Investigator.

17) Known or suspected history of alcohol, drug, or other substance abuse or dependence that in the opinion of the Investigator may interfere with study participation or assessments.

18) Prior exposure to lirentelimab or known hypersensitivity to any constituent of the study drug.

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

20) Subjects who weigh <40 kg at screening.

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

22) Vaccination with live attenuated vaccines within 30 days prior to initiation of treatment in the study, during the treatment period, or vaccination expected within 5 half-lives (4 months) of study drug administration.

    Note: This exclusion criterion does not apply to all types and formulations of vaccines (including live attenuated vaccines) currently authorized/approved by FDA or other regulatory authority for the prevention of COVID-19, which may be administered before, during, or after the study.

    The vaccine should not be administered within 3 days before and within 3 days after the administration of lirentelimab so that any side effects caused by either of the 2 medications can be more easily determined.

23) Employees or relatives of the Sponsor or the Investigator, or other persons dependent on the Sponsor or the Investigator.

24) Commitment to an institution by order issued either by the judicial or the administrative authorities.

25) Presence of a SARS-CoV-2 infection and/or have not completed an authorized/approved COVID-19 primary immunization series as per national recommendations at the time of screening. (Germany only)

Acceptable and required documentation to confirm inclusion and exclusion criteria is further explained in the Study Reference Manual and listed in the eCRF.

8.6 Safety Evaluations

Safety and tolerability will be assessed throughout the study by monitoring and evaluating AE, including any reactions to the SC injection. All TEAE will be collected from the start of study drug administration in the double-blind period of the study through the start of the drug administration in the OLE period, or through Day 169 (±5 days) or ET if subject is not enrolling in the OLE period of the study.

Severity will be assessed using the NCI CTCAE, version 5.0, or most current version. All AE will be assigned a severity grade and will be assessed to determine whether they are clinically significant and related to study drug.

Additional safety evaluations include clinical laboratory tests comprising ADA to lirentelimab, complete blood counts, chemistries, and urinalyses; physical exams; and vital sign measurements.

The Medical Monitor will review blinded safety data throughout the study. Certain safety data (post-treatment cell differentials as well as tissue eosinophil and mast cell counts) will not be provided to study sites or to the Sponsor as it may cause bias. The Safety Monitor will review blinded safety data as well as unblinded cell counts and will escalate to the Medical Monitor as needed in a manner that does not cause bias.

9. Prior and Concurrent Medications

Prior and concomitant medications include both prescribed and over-the-counter medications taken 30 days prior to the screening visit and will be recorded in the electronic Case Report Forms (eCRF). Prior medications and therapies taken for the treatment of AD, even if taken >30 days before the screening visit, will be documented in the eCRF.

For subjects participating in the OLE period, concomitant medications should be recorded in the AK002-018 double-blind treatment period database beginning after the first administration of study drug in the double-blind period of the study up until the first OLE dose is administered after the Day 99 visit.

Any medications that are exclusionary should be discontinued or handled as outlined in Section 9.1 of the protocol.

Subjects should be advised against taking any new medications, both prescribed and over-the-counter, without consulting the Investigator, unless it is required for emergency use, or it is a COVID-19 vaccine.

Immediately prior to the first SC injection, study site personnel should ensure that the subject continues to meet all of the inclusion criteria and none of the exclusion criteria (including use of prohibited medications).

All medications taken for the treatment of AD and any other medications taken during the 30 days prior to screening and during the study must be documented on the eCRF. All medications used to treat IRR or AE during the study must be documented.

All AE, whether elicited by questions from study staff, volunteered, or noted on physical examination/laboratory testing, and regardless of causality or severity, will be assessed and recorded in the eCRF beginning after the first administration of study drug in the double-blind period of the study and ending at the time of study completion or ET of the double-blind period or the OLE period, whichever is later.

9.1 Prohibited Medications

The introduction of medications or therapies for other medical conditions known to affect AD (e.g., systemic corticosteroids, mycophenolate-mofetil, IFN-γ, JAK inhibitors, topical corticosteroids [except when given for rescue therapy], topical calcineurin inhibitors, cyclosporine, azathioprine, methotrexate, phototherapy, or photochemotherapy) are not permitted during the study and during the interval prior to entry into the study as defined in the exclusion criteria.

Prescription emollients or emollients containing additives such as ceramide, hyaluronic acid, urea, or filaggrin are not allowed.

In addition, the use of ultraviolet A or B (UVA or UVB), psoralen + UVA (PUVA), other phototherapy, or tanning beds is not permitted during the study.

The use of 3 or more bleach baths per week is prohibited.

Planned or anticipated major medication procedures or surgeries should be avoided during the study.

Subject will be reminded to not take prohibited medications and to notify the site immediately if a prohibited medication is prescribed by another health care provider. If a prohibited medication is started during the course of the study, the subject may be withdrawn from study treatment and followed for the 12-week follow-up period.

9.2 Allowed Medications

Medications taken for the treatment of AD, such as antihistamines, leukotriene antagonists, and sodium cromolyn, are allowed during the study, unless prohibited (Section 9.1), and doses are to remain stable unless change is required for an unforeseen medical necessity.

During the 7 days prior to Study Day 1, the subject must have used, at least twice daily, 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 the subject was already using a non-medicated topical therapy (i.e., emollient) at the time of screening, the dose, frequency, and type of medication should be maintained throughout the study. If the subject is not using topical emollients at the time of screening, the Investigator will recommend a suitable non-medicated, non-prescription topical emollient/moisturizer that should be maintained throughout the study,

Medicated topical therapy is defined as a topical product that contains an active pharmaceutical ingredient indicated for the treatment of AD (regardless of whether it is an over-the-counter or prescribed product).

All AD medications used during the screening period and throughout the study will be documented in the CRF. Any allowed medications that are taken must remain stable throughout the study.

The use of concomitant medications for other medical conditions (e.g., hypertension, diabetes, acute infections) is permitted during this study. Nasal steroids and inhaled corticosteroids to control asthma are permitted.

All types and formulations of vaccines (including live attenuated vaccines) currently authorized/approved by FDA or other regulatory authority for the prevention of COVID-19 may be administered before, during, or after the study.

The vaccine should not be administered within 3days before and within 3 days after the administration of lirentelimab so that any side effects caused by either of the 2 medications can be more easily determined.

9.3 Rescue Medications

The use or initiation of any topical or systemic therapy for the purpose of treating AD at any point in the study will be considered rescue therapy. Rescue medications are not allowed during the study unless medically necessary at the discretion of the Investigator (i.e., to treat flare-ups of AD symptoms). Rescue treatment for AD symptoms with otherwise prohibited medications may be provided to study subjects at the discretion of the Investigator.

Study subjects requiring topical rescue therapy within the first 4 weeks of Dose 1 of the double-blind period will be discontinued from the study but will be followed for 12 weeks. Subjects

requiring topical rescue therapy after the first 4 weeks following Dose 1 will continue with the dose regimen and be followed through the end of study.

Study subjects requiring systemic rescue therapy during any point in the double-blind period of the study will be discontinued from the study but will be followed for the 12-week follow-up period.

10. Study Treatment

10.1 Formulation of Test Product and Placebo

Lirentelimab SC Drug Product: The lirentelimab drug product is intended for subcutaneous injection. Each drug product vial contains a nominal volume of 1 mL. It is a sterile, preservative-free solution that contains [redacted] lirentelimab in [redacted], pH 6.0 in Water for Injection (WFI). The solution is visually characterized as clear to slightly opalescent, appearing colorless to slightly yellow.

Placebo SC Product: The placebo is intended for subcutaneous injection. Each placebo vial contains a nominal volume of 1 mL. It is a sterile, preservative-free solution that contains [redacted], pH 6.0 in WFI. The solution is visually characterized as clear to slightly opalescent, appearing colorless to slightly yellow.

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

Each dosing (lirentelimab SC or placebo SC) will comprise 1 SC injection of 2 mL of study drug administered in the front of the thigh with a 27-gauge SC needle. Maximum volume administered per SC injection site will be 2 mL.

Lirentelimab SC or placebo SC (based on randomization assignment) will be administered on Day 1 (±3), Dose 1; Day 15 (±5), Dose 2; Day 29 (±5), Dose 3; Day 43 (±5), Dose 4; Day 57 (±5), Dose 5; Day 71 (±5), Dose 6; and Day 85 (±5), Dose 7.

Subjects will have the option to enroll in an OLE period to receive an additional 7 doses of study drug. Subjects will be observed for at least 1 hour after each injection.

Dosing visits must be conducted within the ± windows stipulated in the protocol with the following requirements:

- The interval between dosing visits must be at least 7 days and no more than 21 days from the previous dosing visit unless directed otherwise by Allakos. The interval count starts the day after the visit and includes the day of the next visit.
- The interval between the final dosing visit and the efficacy visit (Day 99) must be at least 11 days and no more than 17 days from the final dosing visit unless directed otherwise by Allakos. The interval count starts the day after the visit and includes the day of the next visit.

10.2 Study Drug Packaging and Labeling

Study drug is supplied in 2R Type I clear glass vials, securely sealed with a fluoropolymer-coated bromobutyl stopper and aluminum flip-off cap. It is intended for SC injection. The vials are packed in cartons, and each carton contains 1 vial.

Each vial and each carton will be labeled with all required details as per the applicable local regulations. The labels will include, among other details, an investigational use statement, lot number, kit number, Sponsor name, and directions for storage. Each vial will also contain a tear-off label with kit number and space to document Patient ID and dispensing/administration date. This tear-off label should be applied to the IP Injection Dispensing Worksheet and maintained with the source documents.

10.3 Supply of Study Drug to the Investigational Site

The Sponsor (or designee) will ship study drug to the investigational sites. The initial study drug shipment will be shipped after all required regulatory documentation and approvals have been received by the Sponsor, the contract has been executed, and the first screened subject is entered into the IRT system. Subsequent study drug shipments will be triggered automatically based on predetermined supply levels and enrollment activity at the site.

10.4 Study Drug Dose and Dosing Regimen

Subjects will be randomly assigned through the IRT system to an active dose group of 7 doses of lirentelimab SC or placebo SC (Table 2). The dose will be assigned at the time of randomization.

Study drug will comprise 1 SC injection of 2 mL administered in the front of the thigh with a 27-gauge needle. Maximum volume administered per SC injection will be 2 mL as indicated in the study Pharmacy Manual on Day 1 (±3), Dose 1; Day 15 (±5), Dose 2; Day 29 (±5), Dose 3; Day 43 (±5), Dose 4; Day 57 (±5), Dose 5; Day 71 (±5), Dose 6; and Day 85 (±5), Dose 7.

Subjects will have the option of going into an OLE period to receive an additional 7 doses of active study drug.

Table 2 Study Drug Dosage

Route	Dose (7 Doses Biweekly Over 12 Weeks)	Injection Volume/Dose
Subcutaneous	300 mg Lirentelimab SC or Placebo SC	2 mL

10.5 Preparation of Study Drug

A study pharmacist or designee will prepare the study drug for each SC injection based on the assigned dose at randomization. On the day of dosing, the designated study pharmacist will prepare lirentelimab or placebo for SC injection. Appropriate aseptic technique will be used, and the drug will be dispensed according to the Pharmacy Manual for AK002-018. Refer to the Pharmacy Manual for additional details.

Lirentelimab does not meet the definition of a "hazardous drug" and therefore is not required to be classified according to the USP Hazardous Drug Grouping. A drug is considered to be hazardous if it exhibits one or more of the following characteristics in humans or animals: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity, organ toxicity at low doses, genotoxicity, or structure and toxicity profiles of new drugs that mimic existing hazardous drugs (USP, 2019). Since lirentelimab is not considered to be a hazardous drug, special precautions do not need to be taken when handling or preparing the study drug.

10.6 Study Drug Administration

Specific instructions on administration and supplies required for administration are detailed in the Pharmacy Manual. In general, study drug will comprise 1 SC injection administered in the front of the thigh with a 27-gauge needle. Subjects will be observed for at least 1 hour after the SC injection and per the Investigator's discretion.

10.7 Study Drug Storage

Study drug will be stored by the study sites at 2°C to 8ºC under lock at the designated clinic/pharmacy location. Access will be restricted to designated clinic/pharmacy staff. If the temperature of study drug storage in the clinic/pharmacy exceeds or falls below this range, the study drug will be quarantined and the temperature excursion will be reported to the Sponsor or designee. The Sponsor will notify the site if the study drug can be released from quarantine.

10.8 Study Drug Accountability

The study pharmacist/designee is responsible for maintaining accurate and current records accounting for the receipt, dispensing, preparation, use, return (or destruction), and final disposition of all investigational product (IP). All dosage assignments and dispensations will be documented on the source documents. The Master IP Accountability Log should be used to capture receipt, dispensing, and return (or destruction). Electronic IP accountability systems may be used, depending on site preference, as long as the same information is captured. The study monitor will verify entries on these documents throughout the course of the study. Study drug will be labeled with kit numbers but will not reveal whether the kit contains active drug or placebo.

11. Subject Numbering, Stratification, Randomization, and Blinding

11.1 Subject Numbering

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

- The first 3 digits designate the study number. For this study, the number is 218.
- The second 3 digits designate the site number.
- The last 3 digits designate the order of consent at the site (the first subject who provides consent is 001, the second subject is 002, etc.).

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

11.2 Stratification and Randomization

To be randomized into the study, the subject must have chronic AD (according to the American Academy of Dermatology Consensus Criteria, Appendix 1) that has been present for at least 3 years before the screening visit. The subject must have an EASI score of ≥16, the subject's AD must involve at least 10% or more of the BSA, along with an IGA score of 3 or above on a scale of 0–4. The subject must also meet all other applicable inclusion criteria and none of the exclusion criteria.

If the subject qualifies for the study after completing all of the screening procedures, on the day of the first SC injection (Dosing Day 1), the site will access the IRT system in order to stratify and randomize the subject in the study. The IRT system will then randomly assign the subject at an allocation ratio to lirentelimab SC 300 mg, or placebo SC for 7 doses in a double-blind manner and will send an email to the pharmacist and/or designee detailing the kit number(s) to use to prepare the SC injection.

The subject will be stratified based on:

1) Biologic-naïve status vs. biologic-exposed status
2) IGA score at baseline: IGA score of 3 vs IGA score of 4

Approximately 130 subjects (65 per arm) will be randomized to treatment with lirentelimab SC or placebo SC. A subject is considered enrolled in the study when the subject receives the first dose of study drug. For subsequent SC injections the coordinator will access the IRT system on the day of SC injection and enter the PID; the system will assign the subject the dose according to the subject's randomization number. The pharmacist and/or designee will then receive an email detailing the kit number(s) to prepare.

Prior to each SC injection, the Investigator or designee will confirm the PID recorded on the SC syringe provided by the pharmacist matches the subject. The patient identification should be confirmed and documented by a second party prior to administering the SC injection(s), whenever possible. There will not be any unblinding information on the IRT notification to the pharmacist or on the vials provided to the site.

The assignment of treatment to lirentelimab SC or placebo SC will be securely retained in the IRT system until such time as designated by the Statistical Analysis Plan (SAP).

11.3 Blinding

The identity of test and control treatments will not be known to Investigators, Sponsor, research staff, subjects, or the study monitor. The following study procedures will be in place to ensure double-blind administration of study treatments:

- Access to the randomization codes will be strictly controlled by the IRT system.
- Throughout the double-blind study, the blind should remain unbroken except for an emergency when knowledge of the subject's study medication is necessary for further management or if required for regulatory reporting. The Allakos Medical Monitor approves any emergency blind break, if at all possible, prior to the unblinding.

- The lirentelimab and placebo for SC injection will be identical in appearance.
- Results from the analysis of blood samples for PK and ADA will not be provided to the Investigator and Sponsor until after final database lock of the double-blind study.
- Results from the analysis of blood samples for histamine/tryptase tests (collected in case of possible anaphylaxis) will not be provided to the Investigator and Sponsor until after final database lock of the double-blind study, unless required for immediate safety reasons.
- Results of the assessments noted below will not be provided to the Investigator and Sponsor until after final database lock of the double-blind study, so as to not introduce bias. The results will be reviewed on an ongoing basis by the Safety Monitor and escalated as appropriate.
  - Differential cell counts including neutrophils, eosinophils, basophils, monocytes, and lymphocytes.

Other than under the conditions described above, the study blind will be revealed on completion of the study as noted in Section 17.4.

11.4 Breaking the Blind

Breaking the blind in a clinical study on an emergency basis by the site should only occur when knowledge of the treatment to which a subject was allocated would have implications for the emergency medical management of the subject, if required for regulatory reporting, or if there is a pregnancy during the pregnancy reporting period.

If necessary, emergency breaking of the blind can be conducted through the IRT by the Investigator or other registered site users and/or the Medical Monitor. Whenever possible, the Investigator should contact the Medical Monitor before an emergency breaking of the blind. Reason for unblinding, person conducting the unblinding, personnel who know the unblinded treatment, and date/time of unblinding will be recorded.

12. Study Procedures and Guidelines

Table 1 provides the schedule of assessments depicting the required testing procedures to be performed for the duration of the study. When multiple evaluations are scheduled at the same time point, the priority for each will be as follows:

- At home: For the daily questionnaires that the subject completes at home, the subject should complete the [redacted] except on days of study visits when the [redacted] will be completed while the subject is at the study site.

- At the clinic:
  1) [redacted] IGA, EASI, [redacted], and Atopic Conditions Questionnaire.
  2) Vital signs will be obtained after the subject has been at rest for ≥5 minutes.
  3) Physical examinations can be performed and urine samples can be collected either before or after other evaluations, unless otherwise specified.

12.1 Pharmacodynamic/Efficacy-Related Procedures

To ensure consistency in grading, the same Investigator should make all assessments for a subject starting from screening and continuing throughout the double-blind period and OLE period of the study whenever possible. It will not be considered a protocol deviation if a different Investigator makes an assessment for a subject during the study, but this should be avoided as much as possible.

12.1.1 Validated Investigator Global Assessment

The validated Investigator Global Assessment (vIGA) 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 (Appendix 2). 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 vIGA is a physician-conducted assessment.

The vIGA will be determined during screening, and a baseline will be established. A vIGA score of ≥3 is required to enroll in the study. The vIGA will be measured by Investigators during screening, predose on all dosing days, and during each follow-up day or ET.

12.1.2 Eczema Area and Severity Index

During screening, the EASI will be determined, and a baseline will be established. The EASI score is a tool used to measure the extent (area) and severity of atopic eczema with respect to erythema, excoriation, infiltration, and lichenification at 4 anatomic sites of the body: lower and upper extremities, trunk, and head (Appendix 3). The total EASI score will be in a range from 0 to 72 points (from no disease to maximum disease severity) and 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 during screening, predose on all dosing days, and during all follow-up on Days 99, 141, and 169 or ET.

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.

12.1.3 [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 (Appendix 4). 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]. The following question will be presented to subjects:

[redacted]

Scale of [redacted]

12.1.4 [redacted]

The [redacted] is a simple measurement of the [redacted] (Appendix 5). At screening, the Investigator will determine the [redacted]. The subject is required to have [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.

12.1.5 [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. 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.

12.1.6 [redacted]

The [redacted] is a [redacted] questionnaire used to measure [redacted] of an affected person (Appendix 6). 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.

12.1.7 Atopic Conditions Questionnaire

On Day 1, Day 99 and OLE Day 99, subjects will be prompted to answer additional questions about severity of symptoms related to asthma, allergic rhinitis and allergic conjunctivitis (Appendix 7).

12.1.8 Photographs

The site staff may take photographs of subjects' AD disease to track study drug response and disease progression. This will depend on the sites' standard operating procedures regarding photography. Subjects will be consented before the Sponsor will have access to any images.

12.1.9 Complete Blood Count with Differential

Blood for complete blood count (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 Days 99, 141, and 169 (±5) or 14, 56, and 84 (±5) days after last dose if ET. The blood sample will be processed and shipped in accordance with the Laboratory Manual and lab kit instructions. A central laboratory will analyze the blood sample and provide results for CBC with differential including hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell count, and absolute differential count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils).

During the double-blind period, all differential blood counts from Day 1 (post-dose) through the end of the subject's participation will be blinded to the Sponsor and the site. An unscheduled CBC may be collected at the request of the Safety Monitor. The blood differential test results (neutrophils, eosinophils, basophils, monocytes, and lymphocytes) will be blinded from the Investigator and Sponsor from post-dose Day 1 through Day 169 or ET and until database lock has occurred. If a subject continues to the OLE period of the study, all differential blood counts will be blinded for the first (OLE Day 1) predose assessments and will be unblinded after the subject has received the first dose of the study drug.

As described in the Investigator's Brochure, changes in certain lab results are a part of the expected effects of lirentelimab and could potentially introduce bias in blinded members of the study. The Safety Monitor will have real-time access to these laboratory results and will review and escalate any concerns/issues to the Medical Monitor and/or the site as appropriate. An

unscheduled CBC with differential may be collected if requested by the Safety Monitor. All panic alerts for blinded values will be sent to the Safety Monitor and evaluated in real time.

12.1.10 Fresh biopsies

Optional lesional and non-lesional biopsy samples will be collected at selected US sites for exploratory analysis at baseline/predose on Day 1 and on Day 99/Week 14 during the double-blind period. These fresh biopsies will be shipped overnight to Allakos for additional cell phenotyping and other exploratory analysis. Once Allakos receives the biopsies, they will be dissociated into single cells and immunophenotyped for immune cell populations (lymphocytes, eosinophils, basophils, mast cells, neutrophils, and macrophages) and other exploratory analysis. Detailed instructions on collection, packaging and shipping will be included in the lab manual. All materials required for shipment of the additional samples will be provided to the site by the Central Laboratory. Subjects who choose to participate will need to sign a separate Information and Consent Form.

12.2 Safety-Related Procedures

12.2.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at screening and at study visits if changes are made. Dose, route, unit, frequency of administration, indication for administration, and dates of medication will be captured. Any prior medication received within 30 days before screening and during the study through Day 169 (56 or 84 [±5] days after last dose of study drug if ET) will be recorded, or through the first dose of study drug if subject enters the OLE period of the study.

For subjects participating in the OLE period, concomitant medications should be recorded in the AK002-018 double-blind treatment period database up until the first OLE dose is administered after the Day 99 visit. Rescue medications and procedures must be documented as rescue treatment in the source documents and on the Prior and Concomitant Medications eCRF.

Any medications taken for AD or AD-related symptoms at any time (even if longer than 30 days before screening) should be listed as concomitant medications, even if the medication was discontinued prior to study participation.

12.2.2 Complete Physical Examination

A complete physical exam will be performed by either the Investigator or a qualified designee during the screening visit. A complete physical exam will 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.

12.2.3 Body Weight and Height

At screening, height (in cm) and weight (in kg) will be measured by the site and recorded. The site cannot use values stated by the subject. Body weight will also be measured on all dosing and follow-up days or 14, 56, and 84 days after last dose if ET.

12.2.4 Symptom-Directed Physical Examination

A symptom-directed physical exam of reported or observed subject symptoms warranting examination in the opinion of the Investigator, including assessments of possible injection site reactions and IRR, will be performed by either the Investigator or a qualified designee at all study visits during the treatment period and follow-up period. New, abnormal physical exam findings must be documented and will be followed by the Investigator or Subinvestigator at the next scheduled visit or sooner if clinically indicated or referred to a non-study physician.

12.2.5 Electrocardiogram

An ECG will be obtained during screening after the subject has been in the resting position for ≥5 minutes and before any blood draw. The Investigator or Subinvestigators will review and assess any abnormalities on the ECG in terms of clinical significance. The ECG (without intensive QT analysis) will be used to identify diseases or conditions that would put the subject at increased risk if participating in a clinical study, so this should be taken into consideration when evaluating eligibility for entry into the study.

12.2.6 Previous AD Diagnosis and Treatments Review

During the screening visit the Investigator or designee will collect documentation supporting the chronic AD diagnosis and ask the subject about the various treatments or methods of symptom control that they have tried in relation to their AD symptoms. The treatments may include medications (prescription or over-the-counter), therapies (i.e., phototherapy) or adaptive behaviors, as well as alternative medicine (i.e., acupuncture or hypnotic therapy). Any previous therapies and medications as related to subjects' AD disease will be recorded in the study CRF.

Required specific source documentation supporting the assessment of inclusion and exclusion criteria regarding history of AD diagnosis and treatments will be the following:

- A chronic AD diagnosis for at least 3 years (Inclusion Criteria #3) should be confirmed by historical medical records from a dermatologist, allergist, or immunologist, or via current documentation from a study dermatologist, allergist, or immunologist.

- Medical records documenting the topical AD treatments and reason for discontinuation are required for Inclusion Criteria #4. Notes from patient interview alone for previous treatment are not sufficient.
- Dermatologist or study doctor's notes regarding AD treatment history are needed for assessing Inclusion criteria # 9 and Exclusion Criteria #2.

More details are provided in the instruction of the Eligibility CRF page.

12.2.7 Vital Signs

Vital signs including systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate will be taken after the subject has been at rest for ≥5 minutes and before any blood draw (except for post-SC injection when vital signs will be obtained as described below).

Vital signs will be measured at screening, on Day 8 (±3), on all follow-up days or 14, 56, and 84 (±5) days after last dose if ET, and on all dosing days within 30 minutes predose, 15 (±5) minutes after completion of the SC injection, and just prior to discharge.

Additional vital signs measurements may be collected at the Investigator's discretion if an IRR occurs. Vital signs including systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate will be measured after the subject has been at rest for ≥5 minutes and before any blood draws have been obtained (unless collected for an IRR).

Please refer to the schedule of assessments in Table 1.

12.3 Clinical Laboratory Measurements

Blood and urine samples for clinical safety laboratory tests will be collected at the time points described below. Investigators may have additional laboratory tests performed for the purpose of planning treatment administration or following AE or abnormal laboratory values.

The site will process and ship blood and urine samples per central laboratory instructions. A central laboratory or designee will analyze blood and urine samples and provide results for the clinical safety laboratory tests.

Clinical laboratory testing may be performed locally, if necessary, with prior approval from Allakos. The site will strive to use the central laboratory whenever possible.

For any laboratory test value outside the reference range, the Investigator will determine clinical significance: Not Clinically Significant (NCS) or Clinically Significant (CS). An abnormal laboratory value should be deemed CS if any of the following conditions are met:

- The abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline.
- The abnormality is of a degree that requires additional active management, e.g., change of study drug dose, discontinuation of the study drug, close observation, more frequent follow-up assessments, or further diagnostic investigation.

Therefore, a clinically significant laboratory value is a lab test value that indicates a new disease process, an exacerbation or worsening of an existing condition, or requires further action to be taken.

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

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

Blood will be obtained for CBC with differential as described in Section 12.1.9.

12.3.1 Blood Chemistry Profile

Blood for chemistry, including hCG and FSH (only for screening), will be collected. Only subjects of childbearing potential and postmenopausal women are required to have hCG or FSH testing (as described in Section 12.3.2). Postmenopausal status must be confirmed by testing of FSH prior to the first dose of study drug regardless of the subject's age.

Blood for chemistry will be obtained predose on all dosing days, as well as during screening, and on Days 99, 141, and 169 or 14, 28, 56, and 84 (±5) days after last dose if ET.

The blood sample will be processed and shipped in accordance with the Laboratory Manual and laboratory kit instructions. A central laboratory will analyze the serum sample and provide

results for chemistry tests including sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, creatine kinase, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), and lactate dehydrogenase.

12.3.2 Pregnancy Test and Follicle-Stimulating Hormone

A serum pregnancy test (hCG level) will be completed for all female subjects of childbearing potential at screening. Women who are surgically sterile (tubal ligation, partial or total hysterectomy, or bilateral oophorectomy) for at least 3 months or those who are postmenopausal for at least 1 year with FSH level >30 mIU/mL are not considered to be of childbearing potential. At screening, FSH levels will be tested on female subjects to confirm postmenopausal status. Both FSH and hCG samples will be processed by the central laboratory.

Subjects with FSH levels ≤30 mIU/mL will be considered to be of childbearing potential. Blood will be collected for serum pregnancy test at screening. 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. If a subject has a positive pregnancy test, dosing will immediately be discontinued.

To ensure subject safety, each pregnancy in a subject that received study drug must be reported within 24 hours of learning of its occurrence. If the subject received lirentelimab SC, the pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence of absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. If the subject received lirentelimab SC, any SAE experienced during pregnancy must be reported on the SAE Report Form.

12.3.3 Effective Methods of Contraception for Allakos Studies

This section applies to study subjects who are women of childbearing potential (WOCBP) and male study subjects whose sexual partners are WOCBP.

Applicable for Study Sites in the United States:

Abstinence is the only birth control method that is 100% effective in preventing pregnancy. For subjects who do not practice abstinence, Allakos requires that study subjects use highly effective methods of contraception, which include:

- Permanent Sterilization: Tubal ligation, vasectomy – 99% effective

- Long-Acting Reversible Contraceptives (LARC):
  - IUD – 99% effective
  - Implantable rod (matchstick sized rod that contains progestin hormone implanted under the skin of the upper arm; prevents ovulation) – 99% effective
- Contraceptive Injection:
  - Intramuscular or subcutaneous injection of progestin hormone every 3 months – 96% effective
- Short-Acting Hormonal Methods:
  - Oral contraceptives or patch – 91% effective
  - Vaginal contraceptive ring (releases 2 hormones, progestin and estrogen, to prevent ovulation) – 91% effective

Note: Effectiveness rates obtained from the Birth Control Guide on the FDA web site (FDA, 2021).

Barrier and other methods not listed above when used together as dual methods such as a condom + diaphragm or condom + spermicide are less effective methods, therefore these dual methods are not recommended as they could increase the risk of becoming pregnant during the study or follow-up period. When using dual methods, at least 1 of the methods should be a highly effective method of contraception.

Applicable for Study Sites in Germany:

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Allakos requires that study subjects use highly effective methods of contraception, which include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]: Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation 1: Oral, injectable, or implantable[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]

- Vasectomised partner[2,3]
- Sexual abstinence[4]

1) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraception method.
2) Contraception methods that in the context of this guidance are considered to have low user dependency.
3) Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
4) In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Note: Recommendations related to contraception and pregnancy testing in clinical trials (version 1.1) by the Clinical Trials Facilitation and Coordination Group (CTFG, 2020).

12.3.4 Urinalysis

Urine will be obtained for urinalysis at screening and on follow-up Days 99 and 169 (14 and 84 [±5] days following last dose if ET), and symptom-based, as necessary. The urine sample will be processed and shipped in accordance with the Laboratory Manual and laboratory kit instructions. A central laboratory will analyze the urine sample for specific gravity, pH, protein, glucose, ketones, blood, and leukocyte esterase.

12.3.5 Serology

Blood will be obtained at screening for serology tests including hepatitis B surface antigen (HBsAG), hepatitis C antibody, hepatitis B core antibody (anti-HBc), and human immuno-deficiency virus (HIV). The blood sample will be processed and shipped to the central laboratory in accordance with the Laboratory Manual and lab kit instructions. A positive result, if clinically significant (and not due to previous vaccination or resolved disease or exposure) will exclude the subject from enrollment (Appendix 10).

12.3.6 Anti-Lirentelimab Antibodies

Blood for determination of ADA will be collected predose on dosing Days 1, 43, and 85 (±5), 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. Additional ADA samples will be collected at each dosing visit during the OLE period.

An unscheduled blood sample for ADA may also be obtained if a related AE suspected of being associated with immunogenicity occurs. The serum sample will be collected, processed, and shipped in accordance with the Laboratory Manual and lab kit instructions. A central laboratory will analyze the sample for anti-lirentelimab antibodies using a validated assay method.

Additionally, the serum samples collected for ADA will be retained for future testing in the event that any new potential safety or immunogenicity issues are identified.

12.3.7 Blood for Pharmacokinetics

Blood samples for serum PK assessments will be collected predose on dosing Days 1, 15, 29, 43, 57, 71, and 85 (±5) as well as on Day 8 (±3) and during follow-up on Days 99, 141, and 169 (±5) or 14, 56, and 84 (±5) days after last dose of study drug if ET. The serum samples will be collected predose and processed and shipped frozen in accordance with the Laboratory Manual and lab kit instructions.

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

12.3.8 Blood for IgE

Blood will be collected for determination of serum IgE levels and sent to the central laboratory for processing. Blood will be collected during screening, predose on Day 57 and Day 85, and on follow-up Days 99, 141, and 169 or 14, 56, and 85 (±5) days after last dose of study drug if ET.

12.3.9 COVID-19 Testing

Testing for COVID-19 is not required for this study but may be implemented by the study site at any time during the study due to safety regulations or procedures. Testing for COVID-19 may be individually mandated by facilities or by state or country (e.g., Germany) regulation, and if required, this will be consented through the site and not listed in the AK002-018 ICF. Testing for COVID-19 may be performed according to the trial site standard procedures and safety regulations.

The risk assessment related to ongoing Covid-19 pandemic will be reviewed on a continuous basis, and measures required for reducing the risk of infection with the novel coronavirus will be taken, as appropriate.

13. Evaluations and Procedures by Visit

Evaluations and procedures by visit are shown in Table 1.

General Information:

- All recorded clock times should utilize a 24-hour clock.
- Procedures for screening may be performed over the course of multiple visits prior to the first SC injection.
- 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 with the following requirements:
  - The interval between dosing visits must be at least 7 days and no more than 21 days from the previous dosing visit unless directed otherwise by Allakos. The interval count starts the day after the visit and includes the day of the next visit.
  - The interval between the final dosing visit and the efficacy visit (Day 99) must be at least 11 days and no more than 17 days from the final dosing visit unless directed otherwise by Allakos. The interval count starts the day after the visit and includes the day of the next visit.
- For Day 8, the visit can occur within a ±3 day window.

13.1 Screening Day (~Day -14)/Screening Period

1) Obtain written informed consent.
2) Assign the participant a PID.
3) Collect demographics.
4) Obtain medical history.
5) Gather and review AD diagnosis and detailed previous treatment history and concomitants medications (Section 12.2.6).
6) Collect body weight (in kg) and height (in cm) along with vital signs.
7) Perform ECG.
8) Conduct complete physical examination.
9) Collect vIGA, EASI, [redacted].

10) Activate daily PRO and have subject complete first PRO (ppNRS) in the clinic. 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.

11) Have subject complete the [redacted] questionnaire and answer 2 [redacted] questions.

12) Collect blood for serology, serum IgE, chemistry (including hCG and FSH, if applicable), and CBC. Female subjects of childbearing potential are required to have hCG measured. Postmenopausal women are required to have FSH measured. If the postmenopausal FSH result is ≤30 mIU/mL, a serum hCG will be required during the screening period.

13) Collect urine for urinalysis.

14) Conduct eligibility assessment and confirm subject is eligible to move forward with screening.

13.2 Day 1 – Randomization/Dose 1/Baseline

Prior to Study Drug Administration:

1) Assess the subject for SAE related to screening procedures.

2) Confirm continuing eligibility and availability of all required medical records and source documents.

3) Document any changes to health status.

4) Document any changes to medical history and concomitant medications.

5) Assess [redacted] compliance. Subject should complete at least four daily PRO questionnaires during the seven days prior to Day 1.

6) Perform urine dipstick pregnancy test if subject is of childbearing potential.

7) Collect body weight (in kg).

8) Perform symptom-directed physical exam, if needed.

9) Complete vIGA, EASI, [redacted]

10) Have subject complete the [redacted] questionnaire, [redacted] (unless already completed), and Atopic Conditions Questionnaire.

11) If consent is obtained, collect biopsy (applicable for selected US sites only).

12) Randomization:

    a) Prior to randomizing the subject in the IRT system, the Investigator will determine subject's IGA score and biologic-naïve vs biologic-exposed status in order to stratify

subject and sign source Eligibility Form. The study coordinator or designee will enter IGA score and biologic status into the IRT on Study Day 1 to stratify the subject.

b) The IRT system will then randomly assign the subject to lirentelimab SC 300 mg or placebo SC in a double-blind manner and will send an email to the pharmacist and/or designee detailing the kit number(s) to use to prepare the injection. See the Pharmacy Manual for detailed SC injection preparations.

13) Collect vital signs within 30 minutes of the start of the SC injection.

14) Collect blood for CBC, chemistry, PK, and ADA just prior to SC injection.

15) SC Injection of Study Drug:

a) Subcutaneous dosing (lirentelimab SC or placebo SC) comprises 1 SC injection administered in the front of the thigh with a 27-gauge needle. Maximum volume administered per SC injection will be 2 mL. See the Pharmacy Manual for SC injection instructions.

b) Collect vital signs 15 (±5) minutes after study drug administration.

16) Post-SC Injection:

a) Collect blood for CBC with differential 1 hour (±15 minutes) after SC injection.

b) Observe the subject for at least 1 hour after study drug administration.

c) Collect vital signs just prior to discharge.

If anaphylaxis is suspected, a sample of blood should be obtained for plasma histamine level and tryptase within 1–2 hours of the onset of symptoms. Also, an unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

13.3 Day 8 (±3)

1) Assess the subject for AE and SAE.

2) Document any changes to concomitant medications.

3) Assess [redacted] compliance.

4) Collect vital signs and body weight (in kg).

5) Collect blood for PK and ADA

6) Perform urine dipstick pregnancy test if subject is of childbearing potential.

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

13.4 Day 15 (±5) – Dose 2

1) Prior to SC Injection:
   a) Assess the subject for AE and SAE.
   b) Document any changes to concomitant medications.
   c) Assess [redacted] compliance.
   d) Complete IGA, EASI, [redacted] assessments.
   e) Have subject complete [redacted] and [redacted] and 2 questions on the [redacted] questionnaire.
   f) Collect body weight (in kg).
   g) Perform urine pregnancy test if subject is of childbearing potential.
   h) Perform symptom-directed physical exam, as needed.
2) SC Injection of Study Drug:
   a) Enter the visit in the IRT and prepare study drug using kit number(s) provided by the IRT. See the Pharmacy Manual for detailed SC injection preparations.
   b) Collect vital signs within 30 minutes prior to the start of the SC injection.
   c) Collect blood for CBC, chemistry, and PK just prior to the SC injection.
   d) Administer SC injection in the front of the thigh.
   e) Collect vital signs 15 (±5) minutes after study drug administration.
3) Post-SC Injection:
   a) Collect CBC with differential 1 hour (±15 minutes) after the SC injection.
   b) Observe the subject for at least 1 hour after study drug administration.
   c) Collect vital signs just prior to discharge.

If anaphylaxis is suspected, a sample of blood should be obtained for plasma histamine level and tryptase within 1–2 hours of the onset of symptoms. Also, an unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

13.5 Day 29 (±5) – Dose 3

1) Prior to SC Injection:
   a) Assess the subject for AE and SAE.

b) Document any changes to concomitant medications.

c) Assess [redacted] compliance.

d) Perform IGA, EASI, [redacted] assessments.

e) Have subject complete [redacted] and [redacted] and 2 questions on the [redacted] questionnaire.

f) Collect body weight (in kg).

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

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

2) SC Injection of Study Drug:

a) Enter the visit in the IRT and prepare study drug using kit number(s) provided by the IRT. See the Pharmacy Manual for detailed SC injection preparations.

b) Collect vital signs within 30 minutes prior to the start of the SC injection.

c) Collect blood for CBC, chemistry, and PK just prior to the SC injection.

d) Administer SC injection in the front of the thigh.

e) Collect vital signs 15 (±5) minutes after the study drug administration.

3) Post-SC Injection:

a) Collect CBC with differential 1 hour (±15 minutes) after the SC injection.

b) Observe the subject for at least 1 hour after study drug administration.

c) Collect vital signs just prior to discharge.

If anaphylaxis is suspected, a sample of blood should be obtained for plasma histamine level and tryptase within 1–2 hours of the onset of symptoms. Also, an unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

13.6 Day 43 (±5) – Dose 4

1) Prior to SC Injection:

a) Assess the subject for AE and SAE.

b) Document any changes to concomitant medications.

c) Assess [redacted] compliance.

d) Perform IGA, EASI, [redacted] assessments.

e) Have subject complete [redacted] and [redacted] and 2 questions on the [redacted] questionnaire.

f) Collect body weight (in kg).

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

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

2) SC Injection of Study Drug:

a) Enter the visit in the IRT and prepare study drug using kit number(s) provided by the IRT. See the Pharmacy Manual for detailed SC injection preparations.

b) Collect vital signs within 30 minutes prior to the start of the SC injection.

c) Collect blood for CBC, chemistry, PK and ADA just prior to the SC injection.

d) Administer SC injection in the front of the thigh.

e) Collect vital signs 15 (±5) minutes after study drug administration.

3) Post-SC Injection:

a) Collect CBC with differential 1 hour (±15 minutes) after the SC injection.

b) Observe the subject for at least 1 hour after study drug administration.

c) Collect vital signs just prior to discharge.

If anaphylaxis is suspected, a sample of blood should be obtained for plasma histamine level and tryptase within 1–2 hours of the onset of symptoms. Also, an unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

13.7 Day 57 (±5) – Dose 5

1) Prior to SC Injection:

a) Assess the subject for AE and SAE.

b) Document any changes to concomitant medications.

c) Assess [redacted] compliance.

d) Complete IGA, EASI, [redacted] assessments.

e) Have subject complete [redacted] and [redacted] and 2 questions on the [redacted] questionnaire.

f) Collect body weight (in kg).

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

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

2) SC Injection of Study Drug:

a) Enter the visit in the IRT and prepare study drug using the kit number(s) provided by the IRT. See the Pharmacy Manual for detailed SC injection preparations.

b) Collect vital signs within 30 minutes prior to the start of the SC injection.

c) Collect blood for CBC, IgE, chemistry, and PK just prior to the SC injection.

d) Administer SC injection in the front of the thigh.

e) Collect vital signs 15 (±5) minutes after study drug administration.

3) Post-SC Injection:

a) Collect blood for CBC with differential 1 hour (±15 minutes) after the SC injection.

b) Observe the subject for at least 1 hour after the end of the SC injection.

c) Collect vital signs just prior to discharge.

If anaphylaxis is suspected, a sample of blood should be obtained for plasma histamine level and tryptase within 1–2 hours of the onset of symptoms. Also, an unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

13.8 Day 71 (±5) – Dose 6

1) Prior to SC Injection:

a) Assess the subject for AE and SAE.

b) Document any changes to concomitant medications.

c) Assess [redacted] compliance.

d) Perform IGA, [redacted] EASI, and [redacted] assessments.

e) Have subject complete [redacted] and [redacted] and 2 questions on the [redacted] questionnaire.

f) Collect body weight (in kg).

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

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

2) SC Injection of Study Drug:

   a) Enter the visit in the IRT and prepare study drug using the kit number(s) provided by the IRT. See the Pharmacy Manual for detailed SC injection preparations.

   b) Collect vital signs within 30 minutes prior to the start of the SC injection.

   c) Collect blood for CBC, chemistry, and PK just prior to the SC injection.

   d) Administer SC injection in the front of the thigh.

   e) Collect vital signs 15 (±5) minutes after study drug administration.

3) Post-SC Injection:

   a) Collect CBC with differential 1 hour (±15 minutes) after the SC injection.

   b) Observe the subject for at least 1 hour after the SC injection.

   c) Collect vital signs just prior to discharge.

If anaphylaxis is suspected, a sample of blood should be obtained for plasma histamine level and tryptase within 1–2 hours of the onset of symptoms. Also, an unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

13.9 Day 85 (±5) – Dose 7

1) Prior to SC Injection:

   a) Assess the subject for AE and SAE.

   b) Document any changes to concomitant medications.

   c) Assess [redacted] compliance.

   d) Perform IGA, EASI, [redacted] assessments.

   e) Have subject complete [redacted] and [redacted] and 2 questions on the [redacted] questionnaire.

   f) Collect body weight (in kg).

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

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

2) SC Injection of Study Drug:

   a) Enter the visit in the IRT and prepare study drug using the kit number(s) provided by the IRT. See the Pharmacy Manual for detailed SC injection preparations.

   b) Collect vital signs within 30 minutes prior to the start of the SC injection.

c) Collect blood for CBC, IgE, chemistry, PK, and ADA just prior to the SC injection.

d) Administer SC injection in the front of the thigh.

e) Collect vital signs 15 (±5) minutes after study drug administration.

3) Post-SC Injection:

a) Collect CBC with differential 1 hour (±15 minutes) after the SC injection.

b) Observe the subject for at least 1 hour after study drug administration.

c) Collect vital signs just prior to discharge.

If anaphylaxis is suspected, a sample of blood should be obtained for plasma histamine level and tryptase within 1–2 hours of the onset of symptoms. Also, an unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

13.10 Day 99 (±5) or 14 Days Post-Dose – Follow-up Visit 1

1) Assess the subject for AE and SAE.

2) Document any changes to concomitant medications.

3) Assess [redacted] compliance.

4) Perform IGA, EASI, [redacted] assessments.

5) Have subject complete [redacted] and [redacted] two questions on the [redacted] questionnaire, and the Atopic Conditions Questionnaire.

6) Collect body weight (in kg).

7) Collect urine for urinalysis.

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

9) Collect vital signs.

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

11) Collect blood for CBC, chemistry, PK, and ADA.

12) Collect blood for total serum IgE.

13) If consent is obtained, collect biopsy (applicable for selected US sites only).

If the subject elects to receive OLE dosing, the OLE period of the study may begin after all Day 99 assessments of the double-blind period have been completed. The start of OLE dosing

may be delayed for up to 7 days after completion of the Day 99 visit. The subject is in the double-blind period of the study until the first OLE dose of lirentelimab is administered.

13.11 Day 141 (±5) or 56 Days Post-Dose – Follow-up Visit 2

1) Assess the subject for AE and SAE.
2) Document any changes to concomitant medications.
3) Assess [redacted] compliance.
4) Perform IGA, EASI, [redacted] assessments.
5) Have subject complete [redacted] and [redacted] and 2 questions on the [redacted] questionnaire.
6) Collect body weight (in kg).
7) Perform urine pregnancy test if subject is of childbearing potential.
8) Collect vital signs.
9) Perform symptom-directed physical exam, as needed.
10) Collect blood for CBC, IgE, chemistry, and PK.

13.12 Day 169 (±5)/End of Study or 84 Days Post-Dose – Follow-up Visit 3

1) Assess the subject for AE and SAE.
2) Document any changes to concomitant medications.
3) Assess [redacted] compliance.
4) Perform IGA, EASI, [redacted] assessments.
5) Have subject complete [redacted] and [redacted] and 2 questions on the [redacted] questionnaire.
6) Collect body weight (in kg).
7) Collect urine for urinalysis.
8) Perform urine pregnancy test if subject is of childbearing potential.
9) Perform symptom-directed physical exam, as needed.
10) Collect blood for CBC, chemistry, PK, and ADA.
11) Collect blood for total serum IgE.
12) Collect vital signs.

For Early Termination (ET): Perform the visit 14, 56, or 84 (±5) days after the last dose of study drug or prior to this, if necessary, to ensure compliance with the visit.

13.13 End of Study Definition

The end of the double-blind, placebo-controlled period of the study is defined as the completion of the last follow-up visit of the last enrolled subject who elects not to participate in the OLE period of the study.

For subjects electing to enter the OLE period of the study, the end of the OLE period of the study is defined as the completion of the last follow-up visit for the last subject.

The enrollment of the last subject in the double-blind period of the study is anticipated to occur in the first half of 2023. The last subject's last follow up visit will be approximately 24 weeks after the date of enrollment if OLE is not elected, or up to 38 weeks after the date of enrollment if the OLE is elected.

Please refer to Section 14.12 for the study ending prematurely.

14. Adverse Event Reporting and Documentation

14.1 Adverse Events

In accordance with 21 Code of Federal Regulation (CFR) 312.32(b) and International Conference on Harmonization (ICH) Guidance E2A, an AE is any untoward medical occurrence in a clinical investigation of a subject administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment.

An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

Examples of an AE include:

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

The following examples are not considered AE:

- Medical or surgical procedure, although the condition leading to the procedure is usually an AE.
- Anticipated day-to-day fluctuations of preexisting medical conditions (including laboratory values) as long as significant worsening from baseline does not occur.
- Signs or symptoms of the disorder being studied unless they become more severe or occur with greater frequency than occurring at baseline.

All AE, whether elicited by questions from study staff, volunteered, or noted on physical examination/laboratory testing, and regardless of causality or severity, will be assessed and recorded in the eCRF beginning after the first administration of study drug in the double-blind period of the study and ending at the time of study completion or ET of the double-blind period or the OLE period, whichever is later.

For subjects participating in the OLE period, AE will be recorded in the CRF of the AK002-018 double-blind treatment period database up until the first administration of lirentelimab in the OLE period and recorded in the CRF of the AK002-018 OLE period database beginning from the time of first administration of lirentelimab ending at the time of study completion or ET of the OLE period.

14.2 Serious Adverse Events

A SAE is defined as an AE that meets that one of the following criteria:

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

Serious adverse events will be assessed and recorded beginning after the first administration of study drug in the double-blind period and ending at the time of study completion or ET of the

double-blind period or the OLE period, whichever is later. If the SAE is related to a screening procedure, it will be captured from the date of the screening procedure.

14.3 Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) for this study include:

- Malignancies confirmed by histopathological report. (Mast cells and eosinophils are part of the normal immune response. By decreasing their function, lirentelimab could theoretically increase the risk of malignancy.)
- Parasitic infections confirmed by positive clinical laboratory test. (Eosinophils are believed to be involved in protecting the body from parasitic infections. Decreasing their function could theoretically increase the risk of parasitic and opportunistic infections.)
- Opportunistic infections (infections known to be more severe or occur more frequently in immunosuppressed populations) as confirmed by positive clinical laboratory test.
- Injection-related reactions and hypersensitivity reactions, including anaphylaxis.

Adverse Events of Special Interest will be assessed beginning after the time of first administration of study drug and ending at the time of study completion or ET of the double-blind period or the OLE period, whichever is later. Any new AESI (or new information related to a previously reported AESI) must be recorded in the AE eCRF and designated as an "AE of special interest."

14.4 Injection-Related Reactions

All AE considered by the Investigator ***to be related*** to the biological substance and occurring within 24 hours of the start of the SC injection of study drug should be captured as 1 IRR. Common symptoms of IRR may include but are not exclusive to:

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

- Hypotension or hypertension

All symptoms experienced by a subject during an IRR will be listed in the eCRF under 1 IRR, unless the Investigator believes a symptom is not part of the IRR, in which case it will be recorded separately. The start time of the IRR will be captured as the start time of the first symptom, and the end time of the IRR will be captured as the end time of the last symptom.

14.5 Injection Site Reactions

All AE considered by the Investigator to be ***related to the SC administration*** of the biological substance ***at the injection site*** and occurring within 24 hours of the start of the injection should be captured as one injection site reaction (ISR).

Common symptoms of ISR include, but are not exclusive to:

- Redness at the injection site
- Itching at the injection site
- Pain at the injection site
- Swelling at the injection site (beyond the bump caused by the volume of drug injected under the skin)
- Bruising at the injection site
- Burning at the injection site

All symptoms experienced by the subject during an ISR will be listed in the eCRF under 1 ISR, unless the Investigator believes a symptom is not part of the ISR, in which case it will be recorded separately. The start time of the ISR will be captured as the start time of the first symptom, and the end time of the ISR will be captured as the end time of the last symptom.

14.6 Anaphylaxis

A suspicion of anaphylaxis will be carefully monitored and treated according to standard of care. Emergency crash cart equipment and medications, including multiple doses of epinephrine, vasopressors, and bronchodilators, will be available at all times during the conduct of the study. To define anaphylactic reactions in a consistent and objective manner, all AE of suspected anaphylaxis will be evaluated using Sampson's Criteria for Anaphylaxis (Appendix 9). The assessment of an AE will be done pursuant to definitions set forth by ICH Good Clinical Practice (GCP) guidelines and applicable regulatory requirements.

If a subject experiences signs or symptoms of anaphylaxis, they should be treated with standard of care, such as diphenhydramine, acetaminophen, methylprednisolone, epinephrine, and other supportive measures along with cessation of the SC injection. A sample of blood should be obtained for plasma histamine level and tryptase within 1–2 hours of the onset of symptoms. Also, an unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

14.7 Evaluating Adverse Events and Serious Adverse Events

14.7.1 Establishing Diagnosis

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., dysuria, urinary nitrites should be reported as a urinary tract infection). If the diagnosis is not known, individual signs and symptoms should be assessed and recorded in the AE eCRF as separate AE. The Investigator (or qualified Subinvestigator) must assign the following AE attributes listed below (Table 3, Table 4, and Table 5) and is responsible for ensuring this information is recorded in the source documentation.

14.7.2 Assessment of Intensity

Investigators will use their clinical judgment as well as the guidelines laid out in the NCI CTCAE (version 5.0 or most current version) tables (Table 3 and Appendix 8) to assess the intensity of each AE and SAE.

Table 3 Adverse Event Severity per CTCAE

Grade	CTCAE Description*
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL).
3	Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	Life-threatening consequences, urgent intervention indicated.
5	Death related to AE.

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

The term “severe” is a measure of intensity, and a severe AE is not necessarily a SAE. When the intensity of an AE changes within the same day, the maximum severity for the event should be

entered into the AE eCRF. If the intensity changes over a number of days, these changes should be recorded separately (i.e., as having distinct onset dates).

14.7.3 Assessment of Causality to Study Drug

The Investigator should use their clinical judgment as well as the guidelines in Table 4 to assess the relationship between study drug and AE.

Table 4 Adverse Event Relationship to Study Drug

Relationship to Study Drug	Comment
Related	There is clear evidence that the event is related to the use of study drug (e.g., confirmation by positive re-challenge test, if possible). Another etiology is considerably less likely.
Possible	The event cannot be explained by the subject's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and study drug administration.
Unlikely/Remote	An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to study drug administration and/or exposure suggests that a causal relationship is unlikely. (For reporting purposes, Unlikely/Remote will be grouped together with Not Related.)
Not Related	The event can be readily explained by the subject's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and study drug.

14.7.4 Assessment of Causality to Study Procedure

The Investigator should use their clinical judgment as well as the guidelines in Table 5 to assess the relationship between study procedure and AE. Assessment of causality to study procedure should include causality to such items as blood draw (as appropriate), or other.

Table 5 Adverse Event Relationship to Study Procedure

Relationship to Study Procedure	Comment
Related	There is clear evidence that the event is related to a study procedure.
Possible	The event cannot be explained by the subject's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and a study procedure.
Unlikely/Remote	An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to any study procedure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related).
Not Related	The event can be readily explained by the subject's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and a study procedure.

14.7.5 Action Taken

Action taken with respect to study drug will be categorized as none, study drug permanently discontinued, study drug temporarily withdrawn, or other (specify).

Action taken with respect to study participation will be categorized as none, withdrawal from study participation, or other (specify).

Action taken with respect to treatment of an AE will be categorized as none, concomitant medication, concomitant procedure, or other (specify).

14.7.6 Assessment of Outcome

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

14.8 Adverse Event Reporting Procedures

14.8.1 All Adverse Events

Any clinically significant AE that is ongoing at the time of study completion or ET will be followed by the Investigator until event resolution, the AE is otherwise explained, not considered clinically significant by the Investigator, or the subject is lost to follow-up.

All AE identified, whether serious or non-serious, will be recorded in the AE eCRF beginning from the first administration of study drug in the double-blind period of the study and ending at

the time of study completion or ET of the double-blind period or the OLE period, whichever is later. Serious adverse events considered related to screening procedures will be recorded in the AE eCRF starting on the date of informed consent. Whenever appropriate, the CTCAE (version 5.0 or most current version) should be utilized for naming common AE (Appendix 8).

14.8.2 Serious Adverse Event Reporting

In the event of any SAE reported or observed during the study, whether or not attributable to the study drug, site personnel must report it immediately (**within 24 hours of becoming aware of the SAE**) by fax or email to the Sponsor, Allakos Inc.

The SAE report forms will be provided to the investigational site to assist in collecting, organizing, and reporting SAE, and forms must be completed with as much information as is available and should be submitted to the Sponsor within 24 hours of becoming aware of the SAE. Serious adverse events must also be recorded on the AE eCRF and designated as "serious."

Even when only minimal information is available for the initial SAE report, the Investigator should try to make a causality assessment, as the causality is used to determine the timing of regulatory reporting requirements. If the Investigator or designee is not available to sign the SAE report on initial submission, they should be contacted by telephone and their assessment documented on the SAE form (with a note stating signature is forthcoming). The Investigator may change their causality assessment based on follow-up information and submit an amended SAE report form. All efforts will be made to obtain accurate and complete medical records for the SAE. All efforts to obtain information should be documented in the subject's source documents.

The site will notify the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) according to its guidelines.

The subject's condition will be followed by the Investigator or designated Subinvestigator until resolution of the condition or a return to baseline levels. If additional visits are required, the subject will be asked to return to the study site for further follow-up. If the condition is still ongoing at the time the subject exits the study, every effort will be made to continue to follow-up with the subject for a reasonable period of time, as determined by the Investigator or until there is a return to baseline or stabilization of the condition. As additional information becomes available, such as hospital discharge notes and subject medical records, the Investigator will be notified and provided with all relevant information.

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

- The event resolves.
- The event stabilizes.
- The event returns to baseline if a baseline value is available.
- The event can be attributed to agents other than the investigational product or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Serious AE must be reported within 24 hours to:

Fax: +1-888-237-7475

Email: SAE@allakos.com

14.8.3 Pregnancy Reporting

Pregnancies are captured if they occur in female subjects or in the sexual partners of male subjects from the time the subject is first exposed to the investigational product and ending at the time of study completion or ET of the double-blind period or the OLE period, whichever is later.

Female subjects must be instructed to discontinue all study drugs and inform the Investigator immediately if they become pregnant during the study. Male subjects must inform the Investigator immediately if their partner becomes pregnant during the study.

The Investigator must report any pregnancy to Allakos within 24 hours of becoming aware of it using the provided pregnancy reporting forms. Female subjects must be immediately discontinued from study drug. An uncomplicated pregnancy will not be considered an AE or SAE, but all pregnancies in subjects who received lirentelimab will be followed through term. For male subjects with female partners who become pregnant, the site will ask the father (the study subject) to provide information about the outcome of the pregnancy and information about the baby. If detailed health information about the mother is requested by Allakos, a Pregnant Partner Information Release Form will be provided to the site for the mother to sign.

Any congenital abnormalities noted at birth in the offspring of a subject who received lirentelimab will be reported as a SAE. If the subject received lirentelimab, the outcome of any pregnancy and the presence or absence of any congenital abnormality will be recorded in the

source documentation and reported to the Medical Monitor and Sponsor via the pregnancy reporting form.

14.8.4 AESI Reporting

Beginning from the time of first SC injection of study drug and ending at the time of study completion or ET of the double-blind period or the OLE period, whichever is later, any new AESI (or new information related to a previously reported AESI) must be recorded in the AE eCRF and designated as an "AE of special interest."

For subjects participating in the OLE period, AESI 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 injection after the Day 99 visit and recorded in the CRF of the AK002-018 OLE period database beginning from the start of the first OLE injection after the Day 99 visit.

An AESI that also qualifies as a SAE (per Section 14.2) must also be reported as a SAE in accordance with Section 14.8.2. Adverse events of special interest that are also SAE must be recorded in the AE eCRF and designated as both "serious" and as an "AE of special interest." These will be reported on the Sponsor-provided SAE forms and should be reported to the Sponsor within 24 hours of site awareness.

14.9 Medical Monitoring

Dr. [redacted] should be contacted directly using the phone number and/or email address below to report medical concerns or for questions regarding safety.

Allakos Medical Monitor

[redacted], MD
Phone: [redacted]
Email: [redacted]

Allakos Backup Medical Monitor

[redacted], MD
Phone: [redacted]
Email: [redacted]

Medical Monitor for Germany

[redacted], MD, PhD
Phone: [redacted]
Email: [redacted]

14.10 Independent Data Monitoring Committee

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.

14.11 Study Withdrawal Criteria

A subject's participation in the study will be discontinued in the event that:

- Occurrence of an exclusion criterion, which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor.
- Rebounding of eosinophil counts to >1500/μL in subjects who entered the study with eosinophil levels >1500/μL and whose eosinophil counts were initially suppressed after study drug, as assessed by the Safety Monitor, may be withdrawn from the study at the instruction of the Medical Monitor.
- Serum transaminases (ALT and/or AST) >3 × ULN and total bilirubin >2 × ULN (confirmed by repeat) without an alternative explanation.
- Elevation of ALT or AST >3 × ULN (confirmed by repeat) with the appearance or worsening of symptoms felt by the Investigator to be potentially related to hepatic inflammation, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and rash.

14.12 Study Stopping Rules

The study may be discontinued prematurely in the event of any of the following:

- A life-threatening AE that is possibly or probably related to treatment.
- A fatal AE that is possibly or probably related to treatment.
- New information leading to unfavorable risk-benefit judgment of the study drug.
- Sponsor's decision that continuation of the study is unjustifiable for medical or ethical reasons.
- Discontinuation of development of the Sponsor's study drug.
- Approval of the national competent authority (i.e. Paul-Ehrlich-Institut or PEI) or the Favorable Opinion/Approval of IEC/IRB for the conduct of the clinical trial is withdrawn.

- The required modification of the maximum insured sum is not possible following a negative change in the assessment of the benefit-risk ratio, if applicable (i.e., for Germany)

Health Authorities and IEC/IRB will be informed about the discontinuation of the study in accordance with applicable regulations. The study may be terminated or suspended on request of Health Authorities or Sponsor.

Study stopping for an individual site or investigator may occur in the event of noncompliance with the protocol or lapse of good clinical practice.

15. Discontinuation and Replacement of Subjects

15.1 Definition of Study Completion

A subject who completes visits through the Day 169 visit will be categorized as having completed the double-blind period of the study.

A subject who completes visits through the Day 99 visit and enters the OLE period of the study will be categorized as having completed the double-blind period of the study.

A subject who completes visits through the OLE Day 169 visit will be categorized as having completed the OLE period of the study.

The study is considered completed when the last subject completes the last study visit.

15.2 Early Discontinuation of Study Drug

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

- Subject withdraws consent.
- An AE that in the opinion of the Investigator results in it being in the best interest of the subject to discontinue study treatment.
- Protocol deviation requiring discontinuation of study treatment.
- Participation in any other study during the duration of this study.
- Use of a non-permitted concomitant drug, which may adversely affect data interpretation in the opinion of the Medical Monitor.

- Loss of ability to freely provide consent through imprisonment or involuntary incarceration or treatment of either a psychiatric or physical (e.g., infectious disease) illness.

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

All subjects who discontinue study drug treatment should be encouraged to continue on study and complete assessments and procedures according to the 12-week follow-up period in Table 1, if possible.

Reasonable attempts will be made by the Investigator to provide reasons for subject withdrawals. The reason for the subject's withdrawal from the study or all attempts to acquire such will be specified in the source documents.

16. Statistical Methods and General Considerations

This section outlines the statistical methods to be used for the analysis of the data from the study. A separate SAP, which must be documented as completed prior to unblinding the study, will describe data handling and statistical techniques in full detail.

Unless specified otherwise, baseline will be defined as the last week of screening before the first SC injection of study drug. All subject data will be listed. When appropriate, summary statistics of number of non-missing values, mean, median, standard deviation, minimum, and maximum will be computed for continuous variables, and summary statistics of number and proportion will be computed for categorical variables. Two-sided 95% confidence intervals (CI) will be provided for the mean and proportion. No formal statistical inferences will be made for safety parameters.

16.1 Sample Size

Approximately 130 evaluable subjects with moderate-to-severe AD will be enrolled. It is hypothesized that the percentage of subjects who achieve EASI-75 at Week 14 are 44% for lirentelimab and 15% for placebo. To detect the treatment difference of 29%, the number of subjects required for 90% power is 55. However, to account for 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.

16.2 Analysis Populations

The **Safety population** is defined as all subjects who are randomized and have received at least 1 SC injection of the study drug.

The primary efficacy analysis population is the **modified Intent-to-Treat (mITT) population**, defined as all randomized subjects who have received at least 1 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).

The secondary efficacy analysis population is the **Per Protocol (PP) population**, defined as mITT subjects who have received all 7 injections of study drug and did not have major protocol violations possibly interfering with interpretation of efficacy and safety findings.

The mITT population will be used for all efficacy analysis. The PP population will be used for the primary endpoint and select secondary endpoint analyses to evaluate the robustness of the efficacy findings. The Safety population will be used for all safety analysis.

The study statistician along with the study team will review protocol deviations to identify subjects to be excluded from the PP population analysis.

16.3 Subject Disposition

Subject disposition and reason for early discontinuation will be tabulated. Subject demographics, baseline characteristics, and treatment exposure will be summarized.

16.4 Demographic and Baseline Characteristics

The following demographic and baseline variables will be summarized:

- Demographics
- Medical history
- Complete physical exam
- ECG at screening
- Screening vital signs and laboratory tests

Neither the subject's initials nor the full date of birth will be documented in the CRF or in the questionnaires.

16.5 Study Drug Exposure

Number and percent (n and %) of subjects who have received 1, 2, 3, 4, 5, 6, or 7 SC injections will be presented.

16.6 Efficacy Analysis

16.6.1 Primary Efficacy Endpoint Analysis

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.

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. 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.

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, 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 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.

16.6.2 Secondary Efficacy Endpoint Analysis

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.

16.6.3 Exploratory Analysis

The following exploratory efficacy endpoints will be analyzed:

- 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]
- Safety and tolerability of up to 7 doses of lirentelimab SC or placebo SC in subjects with moderate-to-severe AD.
- 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 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]

Handling of missing PRO data for less than four data entries per week, other than during Screening, will be addressed in the SAP.

16.6.4 Interim Analysis

An interim analysis will not be conducted for this study.

16.7 Safety Analysis

Adverse Events: All AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA system organ class (SOC) and preferred term. Listings will include all AE collected on study. The summaries of AE will be based on TEAE, defined as an AE reported in the clinical database with a date of onset (or worsening) on or after the start date of the first SC injection of study drug.

16.7.1 Treatment Emergent Adverse Events

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

- Overview of TEAE to include
  - Number (%) of subjects who reported at least 1 TEAE overall, by severity and by relationship
  - 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 of special interest (TEAESI)
- TEAE by preferred term
- TEAE by SOC and preferred term
- TEAE by maximum severity, SOC, and preferred term
- TEAE by SOC and preferred term and relationship to study drug
- TEAE leading to withdrawal by SOC and preferred term
- Serious TEAE by SOC and preferred term
- TEAESI by SOC and preferred term

16.7.2 Anti-Drug Antibodies

Samples will be obtained for testing of ADA at times identified in Section 12.3.6.

16.7.3 Clinical Laboratory Assessments

Samples will be obtained for the clinical laboratory tests identified in Section 12.3, and laboratory tests to be summarized include chemistry, hematology, urinalysis, and lirentelimab ADA. Descriptive statistics will be used to summarize laboratory results at baseline, each visit, and the change from baseline for each visit. In addition, shift tables will summarize the

laboratory results relative to normal reference ranges at baseline and each post-baseline time point.

16.7.4 Vital Signs

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

16.7.5 ECG

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

16.7.6 Physical Exam

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

16.7.7 Concomitant Medications

All medications (prior and concomitant) will be coded using the most current World Health Organization Drug Dictionary. Concomitant medications will be summarized by Anatomical Therapeutic Chemical class and preferred term.

16.7.8 Subject Confidentiality

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

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

17. Data Collection, Retention, and Monitoring

17.1 Data Collection Instruments

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

17.2 Data Management Procedures

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

All procedures for handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for handling and analysis of data for clinical studies.

17.3 Data Quality Control and Reporting

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

17.4 Database Lock/Disclosure of Randomization Code

There will be 2 database locks for the double-blind treatment period of the study:

- A provisional database lock after all subjects complete the Day 99 visit to allow for the analysis of safety and efficacy through Day 99.
- A final database lock after all subjects complete the study to allow for the analysis of any safety data collected after Day 99.

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 or designee.
- All medications are coded to the satisfaction of the Chief Medical Officer or designee.

- 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 for efficacy assessment 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.

17.5 Archiving of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database. At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

17.6 Availability and Retention of Investigational Records

In accordance with 21 CFR 312.62(c), GCP-V § 13 (10), ICH GCP E6 (R2), and all other applicable regulatory requirements, all essential documents at the study site, the Sponsor's organization or the Sponsor's designee should be retained until at least 2 years after the last approval of an application for a marketing authorization in an ICH region, until there are no pending or contemplated applications for marketing authorization in an ICH region, and until at least 2 years have elapsed since the formal discontinuation of clinical development of the tested IMP and at least 10 years after the end of the clinical study, whichever period is longer. Furthermore, the essential documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. The trial master file will be created during the implementation period of a study, maintained on an ongoing basis throughout the duration of the project, and collated at the end of the study. The files will contain folders that may include but are not limited to the following subcategories:

- Financial agreements
- Regulatory documents
- IEC/IRB documents

- Drug Accountability documents
- Correspondence
- Medical Reports
- Subject Data
- Monitoring Visit Reports
- Sample CRF and CRF Guidelines

17.7 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to 21 CFR Parts 50, 56, and 312 and/or ICH GCP Guideline E6. By signing this protocol, the Investigator grants permission to the Sponsor (or designee) and appropriate regulatory authorities to conduct on-site monitoring and/or auditing, IEC/IRB review and regulatory inspections of all appropriate study documentation, providing direct access to source data and documents. Monitoring of all appropriate study documentation may occur off-site, with remote access to study documents if allowed by local regulation, as permitted by individual study site requirements.

18. Administrative, Ethical, and Regulatory Considerations

The study will be conducted in a manner consistent with this protocol, the Declaration of Helsinki (1996 version), IRB/IEC (21 CFR 56 and/or ICH E6), and Obligations of Clinical Investigators (21 CFR 312 and/or ICH E6), Directive 2001/20/EC (April 4, 2001) as well as other applicable local regulations including Germany's Medicinal Products Act (AMG), Germany's GCP Ordinance (GCP-V), etc. The Sponsor, the Investigators, and all subcontracted organizations involved in the study conduct must also comply with all applicable privacy regulations (e.g., HIPAA, GDPR). The study can be initiated only after obtaining competent authority approval and IRB and/or IEC favorable opinion. If the competent authority withdraws the CTA approval or if the IRB withdraws the favorable opinion on the CTA, the conduct of the study will be terminated immediately.

18.1 Protocol Amendments

An amendment must be agreed to in writing by Allakos Inc. and submitted to the health authority as an Investigational New Drug (IND) amendment. An amendment which is considered substantial according to the EC CT-1 guidelines, must be submitted for review to the competent authority and the responsible IEC/IRB and cannot be implemented without prior written competent authority approval and the IEC/IRB favorable opinion. Written approval of a protocol

amendment is not required prior to implementation of changes to the protocol that eliminate immediate hazard to the subject; however, approval must be obtained as soon as possible thereafter. Each protocol amendment must also be signed by the Investigator.

18.2 Independent Ethics Committees/Institutional Review Boards

The protocol and ICF will be reviewed and approved by the IEC/IRB of each participating study site prior to study initiation. A central IRB may be used if permitted by the participating study site. All SAE, regardless of causality, will be reported to the IEC/IRB in accordance with the standard operating procedures and policies of the IEC/IRB, and the Investigator will keep the IEC/IRB informed as to the progress of the study. The Investigator or a designee will obtain assurance of IEC/IRB compliance with regulations.

Any documents that the IEC/IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, ICF, information concerning subject recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IEC/IRB. The IEC/IRB's written unconditional approval of the study protocol and the ICF will be in the possession of the Investigator before the study is initiated. The IEC/IRB's approval of the investigational site must be available to Allakos prior to shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

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

18.3 Informed Consent Form

Prior to study enrollment, all subjects must consent to participate in writing. The process of obtaining the informed consent will comply with all federal regulations, ICH requirements, and local laws.

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

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

18.4 Publications

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

18.5 Clinical Study Registration

This clinical study will be registered on the Clinical Trial Registry Websites, www.ClinicalTrials.gov and www.clinicaltrialsregister.eu.

18.6 Payment to Subjects

All subjects may be compensated for participating in this study, in accordance with the payment amounts per study day stated in the subject's signed ICF approved by the IEC/IRB. In accordance with Section 4.8.3 ICH E6 (R2), financial compensation from the sponsor to participating subjects shall be limited to the reimbursement of any travel expenses incurred (Germany only). If the subject is discontinued from the study prior to the last study visit, the subject will be compensated for each completed study visit on a pro rata basis, as stated in the subject's ICF. Beginning with dosing Day 1, subjects will be compensated for each completed week of daily questionnaires as long as at least 4 questionnaires per week are completed. Subjects may be reimbursed for expenses associated with attending study visits. No additional compensation beyond what is stated in the ICF is permitted.

18.7 Investigator Responsibilities

By signing the Investigator Protocol Agreement page, the Investigator agrees to:

1) Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights, or welfare of subjects.
2) Personally conduct or supervise the study.
3) Ensure that the requirements relating to obtaining informed consent and IEC/IRB review and approval meet country requirements.
4) Report to the Sponsor or designee any AE that occur in the course of the study, in accordance with 21 CFR Part 312.64 and/or ICH Guideline E2A.
5) Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6) Maintain adequate and accurate records in accordance with 21 CFR Part 312.62 and/or ICH Guideline E6 and to make those records available for inspection with the Sponsor (or designee).
7) Ensure that an IEC/IRB that complies with the requirements of 21 CFR Part 56 and/or ICH Guideline E6 as applicable will be responsible for initial and continuing review and approval of the clinical study.
8) Promptly report to the IEC/IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9) Seek IEC/IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the subjects.
10) Comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements listed in 21 CFR Part 312 and/or ICH Guideline E6.

19. References

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20. Appendices

20.1 Appendix 1: Atopic Dermatitis – American Academy of Dermatology Consensus Criteria

- **ESSENTIAL FEATURES**; must be present:
  - Pruritus
  - Eczema (acute, subacute, chronic):
    - Typical morphology and age-specific patterns*
    - Chronic or relapsing history

    Patterns include:
    1) facial, neck, and extensor involvement in infants and children;
    2) current or prior flexural lesions in any age group;
    3) sparing of groin and axillary regions.

- **IMPORTANT FEATURES**; seen in most cases, adding support to the diagnosis:
  - Early age of onset
  - Atopy
    - Personal and/or family history
    - IgE reactivity
  - Xerosis

- **ASSOCIATED FEATURES** ; these clinical associations help to suggest the diagnosis of AD but are too non-specific to be used for defining or detecting AD for research and epidemiologic studies:
  - Atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)
  - Keratosis pilaris / pityriasis alba / hyperlinear palms / ichthyosis
  - Ocular / periorbital changes
  - Other regional findings (e.g., perioral changes / periauricular lesions)
  - Perifollicular accentuation / lichenification / prurigo lesions

- **EXCLUSIONARY CONDITIONS;** it should be noted that a diagnosis of AD depends on excluding conditions such as:
    - scabies
    - seborrheic dermatitis
    - contact dermatitis (irritant or allergic)
    - ichthyoses
    - cutaneous T-cell lymphoma
    - psoriasis
    - photosensitivity dermatoses
    - immune deficiency diseases
    - erythroderma of other causes

Adapted from Guidelines of Care for the Management of Atopic Dermatitis: Part 1. Diagnosis and Assessment Of Atopic Dermatitis, , Journal of the American Academy of Dermatology (Eichenfield, 2014).

20.2 Appendix 2: Validated Investigator Global Assessment

Validated Investigator Global Assessment scale for Atopic Dermatitis

vIGA-AD™

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Notes:

1. In indeterminate cases, please use extent to differentiate between scores.

For example:

- *Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate".*

2. Excoriations should not be considered when assessing disease severity.

20.3 Appendix 3: Eczema Area and Severity Index

How to Use EASI

The EASI scoring system uses a **defined process** to grade the **severity of the signs** of eczema and the **extent affected**:

1. Select a body region

Four body regions are considered separately:

- Head and neck
- Trunk (including the genital area)
- Upper extremities
- Lower Extremities (including the buttocks)

2. Assess the extent of eczema in that body region

Each body region has potentially 100% involvement. Using the table below, give each respective body region a **score of between 0 and 6** based on the percentage involvement. Precise measurements are not required.

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

To aid in your body region grading you can use the **diagrams** in Appendix 1.

3. Assess the severity of each of the four signs in that body region:

1. Erythema
2. Edema/papulation
3. Excoriation
4. Lichenification

Further explanations of these terms can be found in FAQ's (Appendix 4)

Grade the severity of each sign on a scale of 0 to 3:

0	None
1	Mild
2	Moderate
3	Severe

- ✓ Take an average of the severity across the involved region.
- ✓ Half points (1.5 and 2.5) may be used. 0.5 is not permitted – if a sign is present it should be at least mild (1)
- ✓ Palpation may be useful in assessing edema/papulation as well as lichenification

To aid your severity grading, a **photographic atlas** of suggested categories is available in **Appendix 2**

Remember: ***Include only inflamed areas*** *in your assessment; do not include xerosis (dryness), ichthyosis, keratosis pilaris, urticaria, infection (unless there is underlying eczema), or post inflammatory pigmentation changes.*

EASI © Munksgaard 2001, managed by Wiley

Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001 Feb;10(1):11-8

EASI - United States/English
EASI_AU2.1_eng-USori.doc

20.3 Appendix 3: Eczema Area and Severity Index cont.

How to record your scores

The assessed parameters are inserted into a table (example shown below for age≥8 years). The final EASI score ranges from 0-72.

Body region	Erythema	Edema/ papulation	Excoriation	Lichenification	Area score	Multiplier	Score
Head/neck	(+	+	+	)	X	X 0.1	
Trunk	(+	+	+	)	X	X 0.3	
Upper extremities	(+	+	+	)	X	X 0.2	
Lower extremities	(+	+	+	)	X	X 0.4	
The final EASI score is the sum of the 4 region scores							____ (0-72)

Two forms of the EASI scoring system are available depending on the age of the patients. The multipliers for the region score are different in the under 8's version to reflect the relative proportion of body regions in young children:

- Patients 8 years or above
- Patients under 8 years of age.

The forms can be found in appendix 3.1 and 3.2 and also as word documents on the HOME website (www.homeforeczema.org)

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Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001 Feb;10(1):11-8

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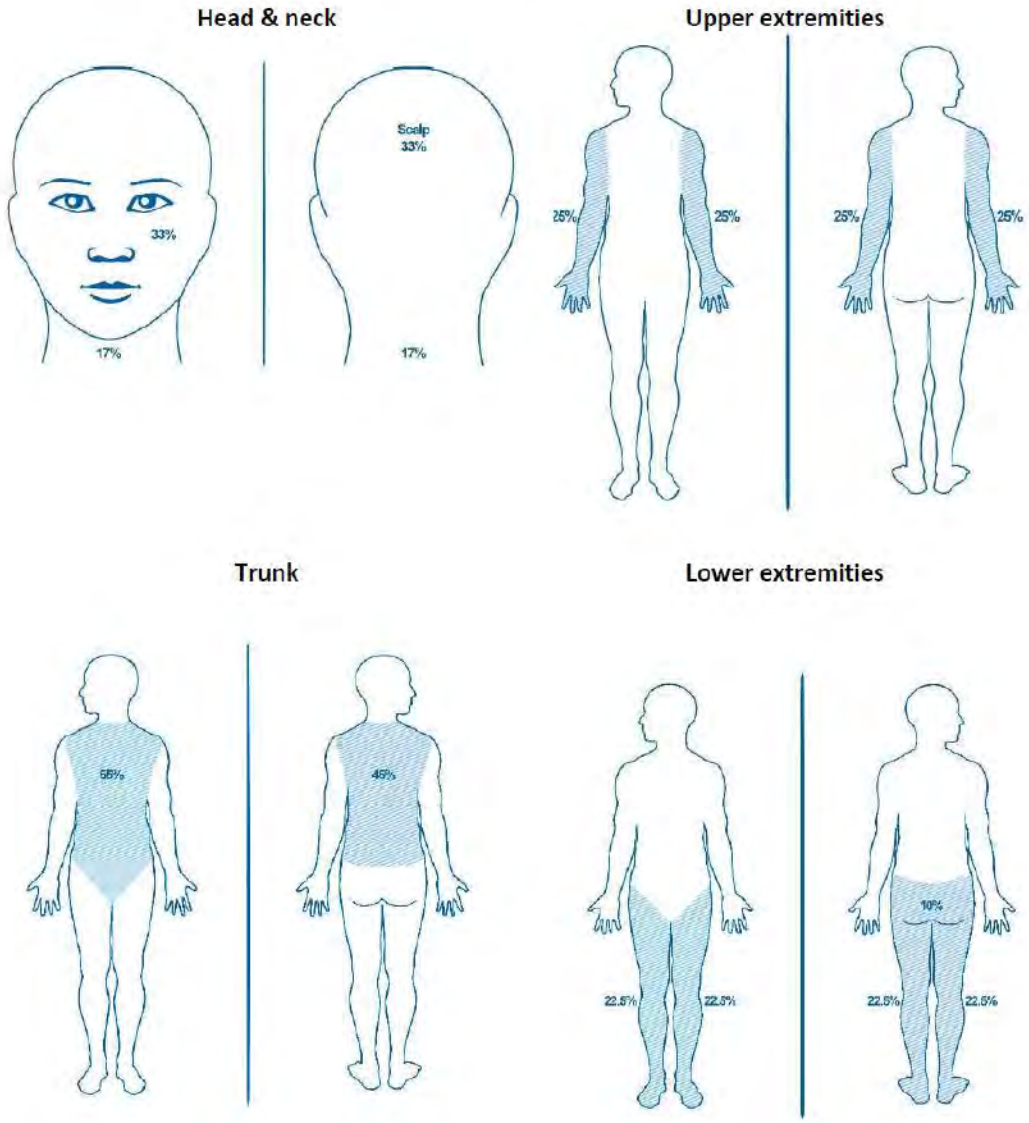
20.3 Appendix 3: Eczema Area and Severity Index cont.

Appendix 1: Eczema Area and Severity Index (EASI) - Extent of eczema per body region

Score each region from 0 to 100%



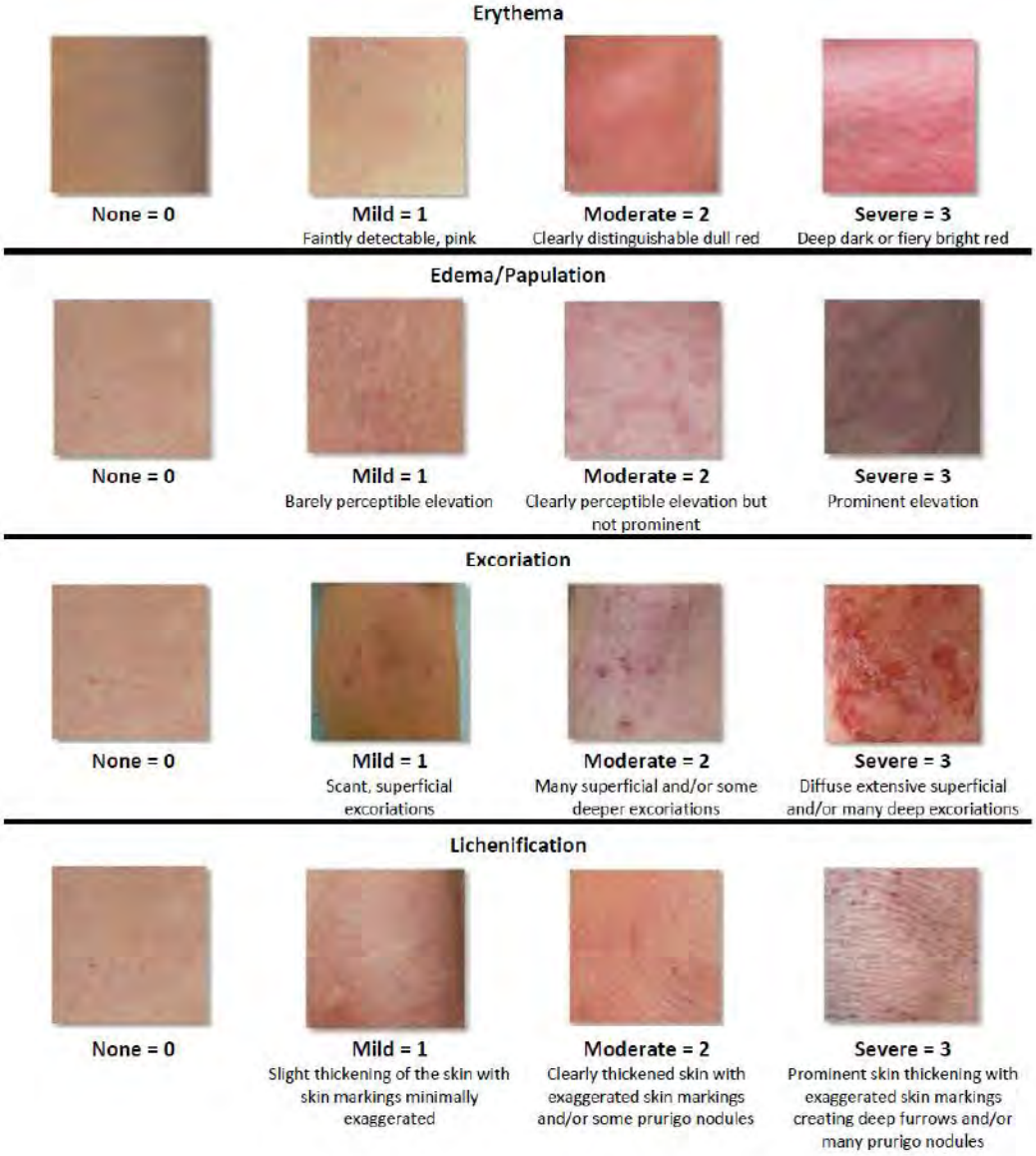
EASI © Munksgaard 2001, managed by Wiley

Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001 Feb;10(1):11-8

EASI - United States/English
EASI_AU2.1_eng-USori.doc

20.3 Appendix 3: Eczema Area and Severity Index cont.

Appendix 2: Eczema Area and Severity Index (EASI) –lesion severity atlas



Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001 Feb;10(1):11-8

EASI - United States/English
EASI_AU2.1_eng-USori.doc

20.3 Appendix 3: Eczema Area and Severity Index cont.

Appendix 3.1: Eczema Area and Severity Index (EASI) case report form – age <8 years

Area of Involvement: Each body region has potentially 100% involvement. Score **0 to 6** based on the following table:

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

Severity of Signs: Grade the severity of each sign on a scale of **0 to 3**:

0	None
1	Mild
2	Moderate
3	Severe

- ✓ Take an average of the severity across the involved area.
- ✓ Half points may be used e.g. 2.5.

Scoring table:

Body region	Erythema (0-3)	Edema/ Papulation (0-3)	Excoriation (0-3)	Lichenification (0-3)	Region score (0-6)	Multiplier	Score per body region
Head/neck	(+	+	+	)	x	X 0.2	
Trunk	(+	+	+	)	x	X 0.3	
Upper extremities	(+	+	+	)	x	X 0.2	
Lower extremities	(+	+	+	)	x	X 0.3	
					The final EASI score is the sum of the 4 region scores:		_____ (0-72)

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Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001 Feb;10(1):11-8

EASI - United States/English
EASI_AU2.1_eng-USen.doc

Appendix 3.2: Eczema Area and Severity Index (EASI) case report form - age≥8 years

Area of Involvement: Each body area has potentially 100% involvement. Score **0 to 6** based on the following table:

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

Severity of Signs: Grade the severity of each sign on a scale of **0 to 3**:

0	None
1	Mild
2	Moderate
3	Severe

- ✓ Take an average of the severity across the involved area.
- ✓ Half points may be used e.g. 2.5.

Scoring table:

Body region	Erythema (0-3)	Edema/ Papulation (0-3)	Excoriation (0-3)	Lichenification (0- 3)	Region score (0-6)	Multiplier	Score per body region
Head/neck	(+	+	+	)	x	X 0.1	
Trunk	(+	+	+	)	x	X 0.3	
Upper extremities	(+	+	+	)	x	X 0.2	
Lower extremities	(+	+	+	)	x	X 0.4	
					The final EASI score is the sum of the 4 region scores:		_____ (0-72)

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Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001 Feb;10(1):11-8

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EASI_AU2.1_eng-USen.doc

20.3 Appendix 3: Eczema Area and Severity Index cont.

Appendix 4 - Frequently Asked Questions

What is the difference between edema/papulation and lichenification?
Consider edema/papulation as corresponding to the acute signs of atopic dermatitis that reflect histological spongiosis. Lichenification are more firm thickened plaques with accentuation of the skin markings that develop as a result of prolonged scratching or rubbing in chronic disease. In darker skin types, follicular lichenification may present as firm flat-topped discrete papules. Grade these chronic lesions as lichenification.

How do I grade prurigo nodules?
Prurigo nodules are larger, deeper lesions as a result of chronic scratching and are graded as areas of lichenification.

How do I grade erythema in darker skin?
To avoid underestimating inflammation in patients with darker skin tones, take into account the underlying skin pigment when grading erythema. Often this means increasing your erythema grade by one level.

Can half-steps be used to assess lesion severity?
The original EASI validation study allowed for half steps. These may be helpful when trying to average the severity of a parameter over a region. For example, if there are some areas with an erythema grading of 2 and some areas more consistent with a severity of 3, 2.5 may be a good choice.

What if most areas in a region are a severity grade of 1, but there are some areas that are a grade 3?
Attempt to average the severity across the involved areas in that region. If these areas are close to equal in size, a score of 2 would be most appropriate. If the majority of involved areas are a grade 1, a score of 1 or 1.5 is more appropriate. Be careful not to score the highest severity in a region but the average one.

How do I grade xerosis (dryness), ichthyosis and hyperlinear palms?
Unless there is active acute or chronic eczema overlying these findings, they are not included in the EASI assessment.

How precise should my assessment of eczema extent be?
The *region scores*, which reflect the extent of eczema, were designed and validated as rough estimates of the percentage of involved skin. Each region is given a *score* ranging from 0 to 6, based on a "ballpark" estimation of extent (see region score table in page 1). If you find it difficult to provide a rough estimate of disease extent, you can use the schematics in Appendix 1 to guide you. More time-consuming methods for evaluating disease extent such as the rule of nines or the 'palm' method are generally unnecessary, as the EASI was designed to be...easy.

Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001 Feb;10(1):11-8

EASI - United States/English
EASI_AU2.1_eng-USori.doc

20.3 Appendix 3: Eczema Area and Severity Index cont.

My patient has responded well to treatment and significantly improved since the last visit. Should I adjust the grading based on the patient's relative improvement?
No. The EASI is a static score, meaning that it is done independently at each time point to reflect current severity. You should grade the EASI per visit regardless of the previous status. Studies have shown that the EASI score has good responsiveness, meaning that overall it is sensitive to change and the improvement will be reflected in the total score.

Can the EASI be used in children?
Yes. The EASI is performed in the same method in all age groups, but the calculation of the final EASI score differs by age. When calculating the EASI, each of the 4 region scores is multiplied by a constant which reflects the relative contribution of that region to the total body surface area. For patients 8 years and older the multipliers are 0.1 for the head/neck, 0.2 for the upper extremities, 0.3 for the trunk and 0.4 for the lower extremities. Below 8 years of age the head/neck multiplier is increased to 0.2 while the lower extremities multiplier decreases to 0.3, consistent with the proportions of these regions in childhood. Refer to Appendix 3 for EASI forms by age.

What happens if a child turns 8 during the course of the study? Which EASI formula should I use?
There are no clear-cut definitions for this situation. In general, if the study is a short term study such as an RCT lasting a few months – using the same formula throughout the trial is preferred, even if the child turns 8 during these months. Keeping the EASI formula consistent in this scenario can serve to preserve the EASI sensitivity to change (e.g. its change in response to treatment) without compromising the validity of the score.
In long term studies such as cohort studies lasting a year or longer, it is important to update the EASI formula based on the physical changes children go through. Switching to the age 8+ formula once a child is older is preferred in that scenario.

What do the terms erythema, edema/papulation, excoriation and lichenification mean?
These are key signs of atopic dermatitis. Recognizing and grading them properly requires training on the visual and physical exam consistent with these signs. Generally speaking, erythema is skin redness; edema/papulation refers to an elevation or swelling of the skin (that should be differed from lichenification below); excoriations are scratch marks that have broken the skin surface; and lichenification is a leathery thickening of the skin with exaggerated skin markings.

Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001 Feb;10(1):11-8

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20.4 Appendix 4: [redacted]

[redacted]

20.5 Appendix 5: [redacted]

[redacted]

20.6 Appendix 6: [redacted]

[redacted]

20.7 Appendix 7: Atopic Conditions Questionnaire

Atopic Conditions Questionnaire

Patient Study ID: 218-_____-_____

▯ Day 1 ▯ Day 99 ▯ OLE Day 1* ▯ OLE Day 99

Instructions: This questionnaire asks about symptoms that people with your condition may have.

Think of the last two weeks and choose the number that best **describes the intensity of your symptoms during that time.**

Please choose an answer by selecting only one box for each question below, as appropriate.

Question #1 Answer only if you have a history of asthma ☐ Not applicable	Over the past two weeks please rate the severity of symptoms of **asthma** at its worst. ☐ 0 – No asthma symptoms ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 – Worst possible asthma symptoms
Question #2 Answer only if you have a history of allergic rhinitis ☐ Not applicable	Over the past two weeks please rate the severity of symptoms of **allergic rhinitis** at its worst. ☐ 0 – No allergic rhinitis symptoms ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 – Worst possible allergic rhinitis symptoms
Question #3 Answer only if you have a history of allergic conjunctivitis ☐ Not applicable	Over the past two weeks please rate the severity of symptoms of **allergic conjunctivitis** at its worst. ☐ 0 – No allergic conjunctivitis symptoms ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 – Worst possible allergic conjunctivitis symptoms

*: Not applicable if OLE Day 1 takes place the same day as the Day 99 of the double-blind period.

Patient signature _____ Date_____

v. 30Nov2022

20.8 Appendix 8: Common Terminology Criteria for Adverse Events v. 5.0

The CTCAE (version 5) for download can be found at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Example of Grading for Administered-Related Reactions

Adverse Event	General Disorders and Administration Site Conditions				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Administered related reaction	Mild transient reaction: injection interruption not indicated; intervention not indicated	Therapy or injection interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of injection); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death

Definition: A disorder characterized by adverse reaction to the injection of pharmacological or biological substances.

Example of Grading for Laboratory Abnormalities

Adverse Event	Grade				
	1	2	3	4	5
Growth hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	–	–	–
Definition: A finding based on laboratory test results that indicate abnormal levels of growth hormone in biological specimen.					
Haptoglobin decreased	<LLN	–	–	–	–
Definition: A finding based on laboratory test results that indicate a decrease in levels of haptoglobin in a blood specimen.					
Hemoglobin increased	Increase in >0–2 g/dL	Increase in >2–4 g/dL	Increase in >4 g/dL	-	-
Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin above normal.					
Lipase increased	>ULN –1.5 × ULN	>1.5–2.0 × ULN; >2.0-5.0 × ULN and asymptomatic	>2.0–5.0 × ULN with signs or symptoms; >5.0 × ULN and asymptomatic	>5.0 × ULN and with signs or symptoms	–
Definition: A finding based on laboratory test results that indicate an increase in the level of lipase in a biological specimen.					
Lymphocyte count decreased	<LLN–800/mm^3; <LLN–0.8 × 10e9/L	<800–500/mm^3; <0.8–0.5 × 10e9/L	<500–200/mm^3; <0.5–0.2 × 10e9/L	<200/mm^3; <0.2 × 10e9/L	–
Definition: A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.					
Lymphocyte count increased	–	>4000/mm^3–20,000/mm^3	>20,000/mm^3	–	–
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.					

20.9 Appendix 9: Sampson's Criteria of Anaphylaxis

ANAPHYLAXIS: Sampson's definition of anaphylaxis (clinical definition) is the acute onset of illness (minutes to several hours) which involves **SKIN, MUCOSAL TISSUE**, **or BOTH** (e.g., generalized hives, pruritus or flushing, swollen lips-tongue uvula) **with 1 OR more of the following** (Sampson, 2006):

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

OR

2 or MORE of the following that occur rapidly after exposure:

- **SKIN, MUCOSAL TISSUE**: e.g., generalized hives, itch-flush, swollen lips-tongue-uvula
- **RESPIRATORY**: Airway compromise (e.g., dyspnea, wheeze, or bronchospasm, stridor and reduced PEF)
- **CIRCULATORY**: Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope)
- **GASTROINTESTINAL**: Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting, nausea, diarrhea)

20.10 Appendix 10: Hepatitis B and Hepatitis C Serologic Testing Details

Hepatitis B Testing Details

HBsAg positive subjects are excluded. However, in case of past infections/vaccinations in order to qualify, the subject's testing status needs to align with the information in Table 6.

Table 6 Hepatitis B Testing

Past Infection (Resolved)			**Vaccinated**	
HBsAg	Negative	***Or***	HBsAg	Negative
Anti-HBc	Positive		Anti-HBc	Negative
Anti-HBs	Positive		Anti-HBs	Positive

Hepatitis C Testing Details

Anti-HCV positive and HCV-RNA positive are excluded. In order to qualify for enrollment, the subject's testing status needs to align with the information in Table 7.

Table 7 Hepatitis C Testing

Non-Reactive			**Past Infection (Resolved)**	
Anti- HCV	Negative	***Or***	Anti- HCV	Positive
			HCV RNA	Negative

20.11 Appendix 11: Open Label Extension Period (Optional)

20.11.1 Summary of the Open-Label Extended Dosing Period

Subjects who complete the double-blind, placebo-controlled treatment period (including the Day 99 study visit) and meet the open-label extended dosing eligibility criteria will be given the option to receive 7 doses of 300 mg lirentelimab SC through the open-label extended (OLE) dosing period.

On Day 99 (±5 days) of the double-blind period, eligible subjects participating in the OLE period will begin following the OLE Schedule of Events (Table 8) and will no longer follow the double-blind period Schedule of Events (Table 1). If OLE Day 1 is completed on the same day as Day 99, already completed assessments (for Day 99) do not need to be repeated (for OLE Day 1), as long as they are performed within time frames noted in the Table 8 notes.

The OLE dosing period is summarized as follows:

- The Investigator will evaluate whether the subject is eligible for OLE. If eligible, the subject will be given the option to participate in the OLE period and receive 7 doses of open-label 300 mg lirentelimab SC administered every 2 weeks starting on Day 99 of the double-blind period, which will be considered Day 1 of the OLE period. OLE dosing may be delayed for up to 7 days after completion of the Day 99 visit.
- On Day 99, after completing all Day 99 assessments, eligible subjects who choose to participate in the OLE period will begin following the OLE Schedule of Events (Table 8).
- Day 1 of the OLE can occur up to 7 days following Day 99 of the double-blind period. In case Day 1 of the OLE is not the same as Day 99 of the double-blind period, applicable subjects (women of childbearing potential) will have a urine dipstick pregnancy test.
- After OLE Day 1, subsequent doses will be given on OLE Days 15, 29, 43, 57, 71, and 85 (±5 days).
- All differential blood counts will be blinded to the Sponsor and the site until after OLE Day 1 dosing.
- 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 be followed for approximately 12 weeks after the last dose. Follow-up visits will occur on OLE Days 99, 141, and 169 (14, 56, and 84 [±5] days) following the last dose of open-label study drug.

- If absolute lymphocyte and/or eosinophil counts have not recovered by the OLE Day 169 visit (last follow-up visit), subjects will return approximately every 28 days for extended follow-up until counts have recovered.

20.11.2 OLE Objective

The objective of the OLE period is to evaluate long-term safety and tolerability of up to 7 doses of open-label AK002 in subjects with AD. The Medical Monitor will review data from the OLE period relating to safety and tolerability throughout the course of OLE dosing.

20.11.3 OLE Eligibility Criteria

Following completion of the randomized, double-blind, placebo-controlled treatment period (including the Day 99 visit), eligible subjects will have the option to receive 7 doses of open-label 300 mg lirentelimab SC through participation in the OLE period.

Subjects who are not eligible or who choose not to participate in the OLE period, will remain in the double-blind study and continue to follow the double-blind period Schedule of Events (Table 1).

20.11.4 OLE Inclusion Criteria

Subjects are eligible to participate in the OLE period if all the following criteria are met:

1) Subject completed the randomized, double-blind, placebo-controlled treatment period, defined as having received all 7 SC injections of study drug (lirentelimab or placebo), and completed the Day 99 visit procedures.

2) Subject is willing and able to comply with the OLE period Schedule of Events (Table 8), including receiving the first open-label 300 mg lirentelimab SC at the Day 99 visit which is 14 days following the last dose of study drug in the double-blind period or up to 7 days after the completion of the Day 99 visit.

3) Subject demonstrates continued eligibility per applicable inclusion criteria (Section 8.4) and exclusion criteria (Section 8.5) of the protocol. “Screening” in Section 13.1. refers only to the screening period completed prior to enrollment in the double-blind treatment period of the study and is not applicable to the OLE period.

20.11.5 OLE Exclusion Criteria

Subjects are not permitted to participate in the OLE period if any of the following criteria are met:

1) Previous administration of the study drug (lirentelimab or placebo) was poorly tolerated by the subject, in the opinion of the Investigator.

2) Any other reason that in the opinion of the Investigator or Medical Monitor makes the subject unsuitable for participation in the OLE period.

Acceptable documentation required to confirm inclusion and exclusion criteria will be further explained in the Study Reference Manual.

20.11.6 OLE Treatment

Formulation, storage, preparation, and administration of the open-label lirentelimab SC for OLE will be consistent with Section 10. of the protocol and the AK002-018 Pharmacy Manual.

The first OLE study drug administration of open-label 300 mg lirentelimab SC will be done on Day 99 of the double-blind period. This will be considered Day 1 of the OLE period. OLE dosing may be delayed for up to 7 days after the completion of the Day 99 visit. The subsequent injections will occur on Days 15, 29, 43, 57, 71, and 85 (±5 days).

The subject will be observed for at least 1 hour (or longer as per Investigator discretion) after the end of the injection. In the event of an IRR, the subject may require prolonged observation (>1 hour or until symptoms resolve), as per Investigator discretion. Subjects will also be instructed to immediately contact the study doctor if any reactions occur after discharge.

20.11.7 OLE Procedures and Guidelines

The OLE period will be conducted in accordance with Table 8 (Schedule of Assessments: Open-Label Extension Period) and the protocol. This includes prohibited medications, study drug preparation and administration, study assessment and procedure guidelines, AE reporting, withdrawal criteria and stopping rules, data collection and management, and ethical and regulatory requirements.

The Investigator will evaluate whether the subject is eligible for the OLE period. On Day 99, eligible subjects that choose to participate in the OLE period will begin following the OLE Schedule of Events (Table 8) and will receive the first open-label dose of lirentelimab.

Table 8 Study AK002-018 Schedule of Assessments: Open-Label Extension Period

Assessment/Procedure Description	OLE Treatment Period (12 weeks)							OLE Follow-Up Period[2] (12 weeks)		
	OLE Day 1 (±5 days) OLE Baseline (Day 99-DB)	**OLE Day 15** (±5 days)	**OLE Day 29** (±5 days)	**OLE Day 43** (±5 days)	**OLE Day 57** (±5 days)	**OLE Day 71** (±5 days)	**OLE Day 85** (±5 days)	**OLE Day 99** (±5 days)	**OLE Day 141** (±5 days)	**OLE Day 169** (±5 days)
	Week 14 **Dose 1**	Week 16 **Dose 2**	Week 18 **Dose 3**	Week 20 **Dose 4**	Week 22 **Dose 5**	Week 24 **Dose 6**	Week 26 **Dose 7**	Week 28 Follow-up 1	Week 34 Follow-up 2	Week 38 Follow-up 3/ EOS[3]
Confirm consent for OLE	X									
Prior/concomitant medications	X[1]	X	X	X	X	X	X	X	X	X
Body weight[4]	X[1]	X	X	X	X	X	X	X	X	X
Vital signs[5]	X	X	X	X	X	X	X	X	X	X
Symptom-directed physical exam[6]	X[1]	X	X	X	X	X	X	X	X	X
vIGA score and dermatologic assessment[7]	X[1]	X	X	X	X	X	X	X	X	X
EASI[7]	X[1]	X	X	X	X	X	X	X	X	X
[redacted][7]	X[1]	X	X	X	X	X	X	X	X	X
[redacted][7]	X[1]	X	X	X	X	X	X	X	X	X
[redacted][7]	<----------Complete daily from screening through OLE Day 169 or 84 days post-last dose---------->									
[redacted]	X[1]	X	X	X	X	X	X	X	X	X
Atopic Conditions Questionnaire[8]	X[1]							X		
Blood for total serum IgE[9]	X[1]				X		X	X	X	X
Blood for chemistry[10]	X[1]	X	X	X	X	X	X	X	X	X
Blood for CBC with differential[11]	X[1]	X	X	X	X	X	X	X	X	X

Assessment/Procedure Description	OLE Treatment Period (12 weeks)							OLE Follow-Up Period[2] (12 weeks)		
	OLE Day 1 (±5 days) OLE Baseline (Day 99-DB)	OLE Day 15 (±5 days)	OLE Day 29 (±5 days)	OLE Day 43 (±5 days)	OLE Day 57 (±5 days)	OLE Day 71 (±5 days)	OLE Day 85 (±5 days)	OLE Day 99 (±5 days)	OLE Day 141 (±5 days)	OLE Day 169 (±5 days)
	Week 14 **Dose 1**	Week 16 **Dose 2**	Week 18 **Dose 3**	Week 20 **Dose 4**	Week 22 **Dose 5**	Week 24 **Dose 6**	Week 26 **Dose 7**	Week 28 Follow-up 1	Week 34 Follow-up 2	Week 38 Follow-up 3/ EOS[3]
Blood for PK[12]	X[1]	X	X	X	X	X	X	X	X	X
Blood for ADA[13]	X[1]			X			X	X		X
Urine for dipstick pregnancy[14]	X[1]	X	X	X	X	X	X	X	X	X
Urine for urinalysis[15]	X[1]							X		X
Eligibility assessment	X									
Study drug administration[16]	X	X	X	X	X	X	X			
Non-serious adverse events[17]	X[1]	X	X	X	X	X	X	X	X	X
Serious adverse events[17]	X[1]	X	X	X	X	X	X	X	X	X

ADA: Anti-lirentelimab antibody [redacted]

CBC: Complete blood count [redacted]

EASI: Eczema Area and Severity Index

EOS: End of Study

FSH: Follicle-stimulating hormone

hCG: Human Chorionic Gonadotropin

IgE: Immunoglobulin E

IRT: Interactive Response Technology

PK: Pharmacokinetics [redacted]

vIGA: Validated Investigator's Global Assessment

Table 8 Notes

1) If OLE Day 1 takes place the same day as Day 99, the following assessments should only be done under Day 99 and not duplicated under OLE Day 1: prior/concomitant medications, body weight, symptom-directed physical exam (if applicable), vIGA, EASI, [redacted] Atopic Conditions Questionnaire, blood for IGE, Chemistry, CBC, PK, and ADA, urine for dipstick pregnancy test (if applicable), and non-serious and serious adverse events. Blood draw and vital sign assessments must follow OLE Schedule of Events (as per below table notes).

2) If absolute lymphocyte and/or eosinophil counts do not recover (to normal range or baseline levels) by OLE Day 169 or ET, extended follow-up visits are required every 14 (±5) days thereafter 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.

Table 8 Notes cont.

3) EOS visits should be conducted 14 (±5) days after the last dose of OLE or prior to this, if necessary, to ensure compliance with the visit. If a subject discontinues the study >14 days after last dose of study drug, the EOS visit should be conducted as soon as possible.

4) Body weight (in kg) will be measured on all dosing and follow-up days (14, 56, and 84 days after the last dose of study drug if ET).

5) Vital signs will be measured on all dosing and follow-up days (14, 56, and 84 days after the last dose of study drug if ET). 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 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 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.

7) The vIGA, EASI, [redacted] will be captured throughout the OLE period. Subjects entering into the OLE period of the study should continue completing the PRO daily. The PRO should be completed around the same time each day.

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

9) Blood samples for total serum IgE will be collected during predose on OLE Days 1, 57, and 85 and on follow-up Days 99, 141, and 169 or 14, 56, and 84 (±5) days after last dose of study drug if ET.

10) 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).

11) Blood for CBC with differential will be obtained just prior to each SC injection, 1 hour (±15 minutes) after the end of each SC injection as well as on all follow-up days (14, 56, and 84 [±5] days after last dose if ET).

12) Blood for PK will be obtained predose on dosing days and on follow-up days (14, 56, and 84 days after the last dose of study drug if ET).

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

14) Urine will be collected for dipstick pregnancy test on all dosing days and follow-up days (14, 28, 56, and 84 days after the 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. If the Day 1 OLE visit does not occur on Day 99 of the double-blind period, then a dipstick urine pregnancy test will have to be done. Day 1 can occur up to 7 days after the Day 99 visit of the double-blind period.

15) Urine for standard urinalysis will be obtained on OLE Day 1 and follow-up Days 99 and 169 (14 and 84 days [±5] if ET) and symptom-based, as necessary.

16) Subjects will remain under observation at the site for at least 1 hour after the end of each SC injection. In the event of an 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.

Table 8 Notes cont.

17) The capture of SAE, non-serious AE, and AESI will be captured through the OLE period until OLE Day 169 or ET. Adverse events will be assessed and recorded in the CRF of the AK002-018 OLE period database beginning from the start of the first open-label SC injection during the OLE Day 1 visit.