

## 1 SYNOPSIS

<b>Protocol Number</b>	AK002-018
<b>Title</b>	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
<b>Sponsor</b>	Allakos Inc.
<b>Clinical Trial Registry Identifiers</b>	EudraCT Number: 2022-001625-79; NCT ID: NCT05528861
<b>IND Number</b>	157566
<b>Indication Studied</b>	Atopic Dermatitis
<b>Investigational Product(s)</b>	<p>Finished Product: Lirentelimab subcutaneous (SC) injection drug product                      Active Ingredient: Lirentelimab (AK002)                      Dose(s): 300 mg                      Mode of Administration: SC                      Batch Number(s):                      Double-blind period:                      Lirentelimab: 0000596831, 000064473                      Open-label extension (OLE):                      000596831, 0000644473, 0000659229                      Duration of Therapy:                      7 doses (1 dose every 2 weeks) in the double-blind period of the study                      7 doses (1 dose every 2 weeks) in the optional OLE period of the study</p>
<b>Reference Therapy</b>	<p>Finished Product: Placebo SC injection drug product                      Active Ingredient: Placebo                      Dose(s): Not applicable                      Mode of Administration: SC                      Batch Number(s): 0000555058, 0000686452                      Duration of Therapy:                      7 doses (1 dose every 2 weeks) in the double-blind period of the study</p>
<b>Investigators and Study Centers</b>	70 sites (55 sites in the United States [IND 157566] and 15 sites in Germany)
<b>Phase and Design</b>	2
<b>Conduct Period</b>	<p>Start Date: 13 June 2022</p> <p>Double-blind Period                      Stop Date: 18 December 2023                      Database Lock Date: 04 January 2024</p> <p>OLE Period                      Stop Date: 13 May 2024 (including the extended follow-up visit to monitor those subjects in European sites with reduced eosinophils at the end of the follow-up period)                      Database Lock Date: 08 May 2024</p>

<b>Number of Subjects (Planned and Analyzed)</b>	It was anticipated that approximately 130 subjects (65 per treatment group) at approximately 70 international investigative sites would be enrolled. The actual number of subjects enrolled was 131 at 40 investigative sites.
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Study AK002-018 was terminated early after all subjects completed the double-blind period due to lack of efficacy of lirtelimumab compared to placebo.

### Compliance Statement

This study was conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.

### Objectives and Endpoints

Tier	Objectives and Endpoints
<b>Primary</b>	<p>The primary objective of the study was to characterize the efficacy of lirtelimumab SC in adult subjects with atopic dermatitis (AD) as assessed by the difference in the proportion of subjects who achieved Eczema Area and Severity Index (EASI)-75 at Week 14.</p> <p>The associated estimand of the primary objective was to measure the effect of therapy with lirtelimumab SC as assessed by the proportion of subjects with EASI-75 response at Week 14 assuming treatment response disappears after subjects were rescued or discontinued from the study or treatment.</p>
<b>Secondary</b>	<p>To further characterize the efficacy of lirtelimumab SC in adult subjects with AD as measured by the following:</p> <ul style="list-style-type: none"> <li>• Percent change in EASI from baseline to Week 14.</li> <li>• Proportion of subjects with Investigator Global Assessment (IGA) of 0 or 1 and a 2-point improvement at Week 14 vs baseline.</li> </ul>

### Safety Objectives

To evaluate the safety and tolerability of lirtelimumab subcutaneous (SC) in subjects with atopic dermatitis (AD) by determining adverse event (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.

### Open-label Extension Objective

The objective of the open-label extension (OLE) period was to evaluate long-term safety and tolerability of up to 7 doses of lirtelimumab SC in subjects with moderate-to-severe AD who completed Day 99 study visit. In addition, the OLE period provided subjects randomized to placebo in the double-blind period the option to receive active dosing.

### Methodology

This Phase 2, proof-of-concept, randomized, double-blind, placebo-controlled study investigated the efficacy and safety of lirtelimumab SC in adult subjects with moderate-to-severe AD inadequately controlled by topical treatments. Approximately 130 subjects were planned to be enrolled in up to 70 sites in the US and Germany and were randomized 1:1 to receive either 7 SC injections of placebo or lirtelimumab every 2 weeks and followed for 12 weeks after the last dose. Subjects were given the option to enroll into the OLE period of the study after completing the

Day 99 visit of the double-blind period. Subjects who opted not to enter the OLE period were followed for 12 weeks after the last dose in the double-blind period.

The study was designed as follows:

- A 14-day screening period with baseline evaluations for study eligibility.
- During the screening period, the Eczema Area and Severity Index (EASI), Peak Pruritus Numeric Rating Scale (ppNRS), and Scoring Atopic Dermatitis (SCORAD) were determined, and a baseline was established.
- If subjects met eligibility criteria, they were stratified based on biologic-naïve vs biologic-exposed status and Investigator Global Assessment (IGA) score at baseline (IGA score of 3 vs IGA score of 4; approximately 40% of the study population were subjects with an IGA of 4). The Interactive Response Technology (IRT) system assigned subjects 1:1 to receive 7 doses of 300 mg lirentelimab SC or placebo SC.
- Eligible subjects received the first dose of lirentelimab SC or identical placebo on Day 1. If the study drug was well tolerated (no stopping rules being met), subjects received 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 were given an option of entering the OLE period and received 7 additional doses of open-label study drug.
- Subjects were followed for 12 additional weeks or 84 days after last dose if early termination (ET), after the double-blind period or the OLE period.
- Subjects remained at the site for at least 1 hour of observation following the end of the SC injection.
- Subjects completed a number of assessments and questionnaires, including daily electronic Patient Reported Outcome (ePRO), throughout the duration of the study.
- Total study duration was approximately 7 months for the double-blind period and 9 months if the subject chose to enter the OLE period.

For eligible subjects who opted for OLE treatment, the first OLE study drug administration of open-label 300 mg lirentelimab SC occurred on Day 99 after completion of the Day 99 visit assessments for the double-blind period. This was considered Day 1 of the OLE period. OLE dosing was allowed to be delayed for up to 7 days after the completion of the Day 99 visit. The subsequent injections occurred on OLE Days 15, 29, 43, 57, 71, and 85 ( $\pm 5$  days). Subjects remained 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. After the last OLE dose, subjects entered 12-week safety follow-up period.

If absolute lymphocyte and/or eosinophil counts had not recovered by the OLE Day 169/EOS visit (last scheduled follow-up visit 12 weeks after the last dose of study drug), subjects returned, for an extended safety follow-up visit approximately every 28 days for up to an additional 8 weeks. If the absolute lymphocyte and/or eosinophil count had not returned to normal or to baseline at the final extended follow-up visit (Day 225 $\pm 7$  days), and the Investigator did not

consider the lymphocyte and/or eosinophil count clinically significant, the subject was discharged from the extended follow-up period. However, if at the final extended follow-up visit (Day 225  $\pm$ 7 days), the Investigator considered the reduced lymphocyte and/or eosinophil count clinically significant, the subject would have been referred for additional evaluation and follow-up with their treating physician. If extended follow-up was required, data collection was limited to hematology, SAE, and AESI.

### **Diagnosis and Main Criteria for Inclusion**

Subjects were eligible for the study if all of the following criteria were 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  $\geq 18$  and  $\leq 80$  years at the time of signing the informed consent form.
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, Janus kinase (JAK) inhibitors, or phosphodiesterase-4 (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  $\geq 16$  at screening and at baseline.
7. Involvement of at least 10% or more of body surface area (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

Subjects were excluded from the study if they met 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. Used 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 was longer.
  - Tumor necrosis factor 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 was longer.
5. Used 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 was obtained that was not treated with or had 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 were 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 was longer, for biologic products).
20. Subjects who weighed <40 kg at screening.
21. Any other reason that in the opinion of the Investigator or the Medical Monitor made the subject unsuitable for enrollment.
22. Vaccinated 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.

## Key Statistical Methods

### Analysis Populations

- The **Intent-to-Treat (ITT) population** included all subjects who were randomized to treatment.
- The **Safety population** included all subjects who were randomized and had received at least 1 SC injection of the study drug. The Safety population was used for all safety analysis.
- The **Modified Intent-to-Treat (mITT) population** included all randomized subjects who had 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 numbers 3, 4, 6, 7, 8 or meeting exclusion criterion number 8 in this study). The mITT population was used for all efficacy analysis.
- The **Per Protocol (PP) population** included all randomized subjects in the mITT population who had received all 7 injections of study drug and did not have major

protocol violations. The PP population was used for the primary endpoint and select secondary endpoint analyses to evaluate the robustness of the efficacy findings.

### Primary Endpoint Analysis

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

H<sub>0</sub>: No treatment difference between lirtelimumab SC and placebo.

H<sub>1</sub>: There is a treatment difference between lirtelimumab SC and placebo.

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

The primary efficacy analysis was performed on the mITT population, as well as the PP population as a supporting analysis.

The primary responder endpoint was 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.

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

- If a subject withdraws from the study, this subject was 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 was specified as a non-responder from the time the rescue medication/rescue treatment was used.
- If the subject has the missing value at Week 14, it was counted as a non-responder at Week 14.

### Secondary Endpoint Analysis

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

Mixed Model for Repeated Measures (MMRM) analyses were performed on continuous endpoints to mitigate the impact of missing data.

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

### Safety Analysis

The summaries of AEs were based on treatment-emergent adverse event (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.

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

- Overview of TEAE
  - 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 (PT)
- TEAE by system organ class (SOC) and PT
- TEAE by maximum severity, SOC, and PT
- TEAE by SOC and PT and relationship to study drug
- TEAE leading to withdrawal by SOC and PT
- Serious TEAE by SOC and PT
- TEAESI by SOC and PT

### Additional Key Analyses

No interim analysis was conducted for the double-blind portion of this study.

### Changes in the Conduct of the Study

Overall, 6 global and 3 local protocol amendments were done over the course of the study. Amendment dates are listed below. Additionally, on 17 January 2024, a letter was sent to all active sites informing them that the study did not meet the primary endpoint and, consistent with the Study Stopping Rules of the protocol, the Sponsor was stopping the study with immediate effect. Investigators were instructed to stop further injections of lirentelimab in subjects that were still in the OLE period of the clinical trial and have these subjects enter the 12-week safety follow-up period as soon as possible.

Protocol	Date	Region(s)
Original	17 August 2021	Global: USA
Amendment 1	08 October 2021	Global: USA
Overall Rationale for the Amendment: Key changes in this amendment included adding a section on estimand, clarification of the allowed and rescue medication and of the stratification and randomization rules, revisions in the visit windows and interval between doses, clarification of sample size and efficacy analysis, and revisions and additions of protocol appendices. Minor text and formatting edits were also made throughout the document for clarity and consistency.		
Amendment 2	18 April 2022	Global: USA and Germany

Protocol	Date	Region(s)
<p>Overall Rationale for the Amendment: The protocol has been amended to gather additional data on subjects with AD who are biologic-naïve and biologic-exposed and to modify the lirentelimab SC dosage and dosing regimen. Minor text and formatting edits were also made throughout the document for clarity and consistency.</p> <p>Key changes included decrease in the total number of subjects; increase in the number of study site and addition of Germany; revision of the study inclusion and exclusion criteria; change in the stratification criteria; revision of dosing regimen; revision of primary, secondary and exploratory objectives/endpoints; clarification of continuous safety review and of grading assessments; addition of section describing effective methods of contraception; addition of OLE dosing period; further clarification of the visit window; removal of 3 patient-reported outcome questionnaires in appendices; and addition of optional biopsies.</p>		
Amendment 3	30 June 2022	Global: USA and Germany
Amendment 3.1	05 October 2022	Germany only
Amendment 3.2	26 October 2022	Germany only
<p>Overall Rationale for the Amendment: The protocol has been amended to gather additional data on subjects with AD who are biologic-naïve and biologic-exposed and to modify screening and enrollment requirements; and to add appropriate language required for submission to Germany regulatory authorities and sites. Minor text and formatting edits were also made throughout the document for clarity and consistency.</p> <p>Key changes included updates of the most common TEAEs; revision of number of subjects and rationale; revisions of medication that should be discontinued at the time of screening, prohibited medication, and allowed medication; edits of study design; revision of the study inclusion and exclusion criteria; clarification of collection of samples for PK and ADA evaluations; revision of primary, secondary, and exploratory objectives/endpoints; clarification of continuous safety review; further clarification of the visit window; and revisions of Schedule of Events table.</p>		
Amendment 4	09 December 2022	Global: USA and Germany
<p>Overall Rationale for the Amendment: Key changes in this amendment included adding an Atopic Conditions Questionnaire to the assessments, specifying the patient-reported outcome requirements during screening, specifying pregnancy testing requirements, adding enrollment monitoring language for EASI score, adding a Body Surface Area form in the appendix, editing definitions in the statistical methods, adding language for independent statistical review committee and stopping rules, and updating safety reporting details.</p>		
Amendment 5	25 July 2023	Global: USA and Germany
<p>Overall Rationale for the Amendment: Key changes in this amendment included updates on language to reflect the required source documents for study entry, revision of statistical analysis including the Interim Analysis, and updates to the description of the investigational products.</p>		
Amendment 6	08 September 2023	Global: USA and Germany
<p>Overall Rationale for the Amendment: The protocol has been amended to remove interim analysis due to the enrollment status, and to align the pre-protocol analysis definition with regulatory guidance.</p> <p>Key changes in this amendment included the removal of the interim analysis and updated definition of per protocol population.</p>		
Amendment 6.1	21 February 2024	Germany only
<p>Overall Rationale for the Amendment: The protocol has been amended to replace Allakos medical monitor and remove back-up medical monitor.</p> <p>Key changes included the addition of 2 extended safety follow-up visits to monitor lymphocyte and eosinophil counts, if necessary, until the expected complete elimination of lirentelimab in the systemic circulation.</p>		

### Subject Disposition

A total of 131 subjects (65 subjects in the lirentelimab group and 66 subjects in the placebo group) were randomized in Study AK002-018, and 130 subjects (65 subjects each) received at least 1 dose lirentelimab or placebo during the double-blind period of the study (Table 14.1.1a).

The majority of subjects (115 [88.5%] subjects overall, 57 [87.7%] subjects in the lirtelimumab group and 58 [89.2%] subjects in the placebo group) completed the study. Of the 16 (12.3%) subjects (8 subjects each in the lirtelimumab and placebo groups) who discontinued study participation, 6 (4.6%) subjects (3 subjects each in the lirtelimumab and placebo groups) discontinued due to an AE, 5 (3.8%) subjects (3 subjects in the lirtelimumab group and 2 subjects in the placebo group) were lost to follow-up, 4 (3.1%) subjects (1 subject in the lirtelimumab group and 3 subjects in the placebo group) withdrew consent, and 1 (0.8%) subject (in the lirtelimumab group) used non-permitted concomitant drugs and treatments.

A summary of subject disposition is presented in Table 14.1.1b for the ITT population, Table 14.1.1c for the Safety population, Table 14.1.1d for the mITT population, and Table 14.1.1e for the PP population.

A total of 16 (12.2%) subjects (5 [7.7%] subjects in the lirtelimumab group and 11 [16.7%] subjects in the placebo group) had at least 1 major protocol deviation during the double-blind period of the study, which were related to inclusion/exclusion criteria (8 subjects total, 4 subjects each in the lirtelimumab and placebo groups), study assessments/study visits (5 subjects in the placebo group), informed consent (2 subjects in the placebo group), and handling/storage/retention of investigational product (1 subject in the lirtelimumab group; Table 14.1.2, Listing 16.2.1.2).

All 131 randomized subjects were included in the ITT population (Table 14.1.3). A total of 130 subjects were included in the Safety population (subjects who were randomized and received at least 1 SC injection of the study drug), with 65 (100%) subjects in the lirtelimumab group and 65 (98.5%) subjects in the placebo group. The mITT population included 122 subjects, with 61 (93.8%) subjects in the lirtelimumab group and 61 (92.4%) subjects in the placebo group. The PP population included 107 subjects, with 53 (81.5%) subjects in the lirtelimumab group and 54 (81.8%) subjects in the placebo group. A summary of reasons for exclusion from the mITT and PP populations is presented in Table 14.1.4.1 and Table 14.1.4.2, respectively.

#### OLE Period

A total of 113 subjects entered the OLE portion of the study, and 112 subjects received study drug; of these, 57 subjects rolled over from the placebo group and 55 subjects continued lirtelimumab treatment from the double-blind period of the study (OLE Table 14.1.1). Subjects in the OLE period received up to additional 7 doses of open-label 300 mg lirtelimumab SC. A total of 66 (58.9%) subjects completed the OLE period and 2 (1.8%) subjects at study sites in Germany were ongoing at the time of the database lock date. For these subjects, the safety follow-up period was extended to continue monitoring absolute eosinophil and/or absolute lymphocyte count until they reach the lower limit of normal per EU laboratory ranges. If at the final extended follow-up visit (Day 225 ±7 days), the Investigator considered the reduced lymphocyte and/or eosinophil count clinically significant, the subject would have been referred for additional evaluation and follow-up with their treating physician. If extended follow-up was required, data collection was limited to hematology, SAE, and AESI. The last 2 subjects in the safety follow-up period completed the study at OLE Day 225.

Of the 44 (39.3%) subjects who discontinued study participation (21 subjects in the placebo rollover group and 23 subjects in the lirtelimumab continuing group), 17 (15.2%) subjects withdrew consent, 14 (12.5%) subjects discontinued due to Sponsor decision, 9 (8.0%) subjects

were lost to follow-up-, 2 (1.8%) subjects discontinued due to an AE, 1 (0.9%) subject discontinued due to use of non-permitted concomitant drugs and treatments, and 1 (0.9%) subject discontinued due to other reason. No meaningful differences in the reasons for study discontinuation were observed between the treatment groups in the OLE period (OLE Table 14.1.1).

A total of 4 (3.6%) subjects (1 subject in the placebo rollover group and 3 subjects in the lirentelimab continuing group) had at least 1 major protocol deviation during the OLE period (OLE Table 14.1.2). The protocol deviations were related to study assessment/study visits (2 subjects in the lirentelimab continuing group), study restrictions/prohibited medications/withdrawal criteria (1 subject in the lirentelimab continuing group), and dose formulation/dose administration/overuse/misuse (1 subject in the placebo rollover group). The protocol deviations in these subjects are further described in OLE Listing 16.2.1.2.

## Summary of Results

### Demographics

Treatment groups of the Safety population were generally well balanced with regard to age, ethnicity, race, height, weight, and body mass index (Table 14.1.5a). The majority of subjects were female (71 [54.6%]), not Hispanic or Latino (80 [63.0%]), and White (78 [60.0%]). The mean age was 42 years (range: 19 to 76 years), and the mean body mass index was 29.0 kg/m<sup>2</sup> (range: 17.2 to 55.8 kg/m<sup>2</sup>). Demographic characteristics within the mITT and PP populations were comparable to those of the Safety population (Table 14.1.5b and Table 14.1.5c, respectively).

Demographics in the OLE period remained consistent with the double-blind period of the study (OLE Table 14.1.3). The majority of subjects were female (67 [59.8%]), not Hispanic or Latino (69 [62.2%]), and White (68 [60.7%]). The mean age was 41 years (range: 19 to 76 years), and the mean body mass index was 29.5 kg/m<sup>2</sup> (range: 17.1 to 55.0 kg/m<sup>2</sup>).

### Baseline disease characteristics

Baseline disease characteristics including, but not limited to, ppNRS, IGA score, EASI score, SCORAD score, BSA affected by AD, and DLQI total score were collected at study entry (Table 14.1.11a).

Overall, there were no clear differences in baseline disease characteristics between the treatment groups during the double-blind period of the study. The majority of subjects (83.1%) were biologic-treatment naïve. The mean and median duration of AD at study entry were 21.7 and 21.3 years, respectively (range: 3.1 to 58.9 years). All subjects had moderate or severe EASI (14.6% and 85.4%, respectively) and an IGA score of moderate or severe (50.8% and 49.2%, respectively). The mean EASI and IGA scores at baseline were 29.1 (range: 16.0 to 67.9) and 3 (range: 3 to 4), respectively.

Baseline disease characteristics of the mITT and PP populations are summarized in Table 14.1.11b and Table 14.1.11c, respectively.

A summary of baseline EASI score by subgroups is presented in Table 14.1.15a for the Safety population, Table 14.1.15b for the mITT population, and Table 14.1.15c for the PP population.

All subjects (100%) had at least 1 medical history condition (Table 14.1.6.a). The most frequently reported medical history conditions ( $\geq 20\%$  of subjects overall) were within the Medical Dictionary for Regulatory Activities SOCs of skin and subcutaneous tissue disorders (100%); respiratory, thoracic, and mediastinal disorders (53.3%); immune system disorders (49.2%); surgical and medical procedures (30.0%); metabolism and nutrition disorders (27.9%); infections and infestations (27.9%); vascular disorders (27.7%); and psychiatric disorders (22.1%). By PT, the most frequently reported medical history conditions ( $\geq 30\%$  of subjects overall) were asthma (37.7%), and seasonal allergy (34.4%). Medical history of the mITT population is summarized in Table 14.1.6b.

All subjects (100%) received medications prior to study entry (Table 14.1.8.1). The most frequently used medications prior to study entry ( $\geq 30\%$  of subjects overall) were soft paraffin and fat products (77.7%), moderately potent corticosteroids (group II) (64.6%), potent corticosteroids (group III) (43.8%), and weak corticosteroids (group I) (35.4%).

All subjects (100%) used concomitant medications during the study (Table 14.1.8.2). The most frequently used concomitant medications ( $\geq 20\%$  of subjects overall) were soft paraffin and fat products (74.6%), selective beta-2-adrenoreceptor agonists (23.1%), and piperazine derivatives (20.0%).

A total of 48.5% of subjects had newly initiated medications during the study (i.e., medications started after the first dose of study drug) (Table 14.1.8.3). The most frequently reported newly initiated medications ( $\geq 10\%$  of subjects overall) were anilides (13.8%) and moderately potent corticosteroids (group II) (10.8%).

AK002-018 baseline disease characteristics during the OLE period remained generally consistent with the double-blind period of the study (OLE Table 14.1.5.1). A summary of OLE baseline disease characteristics is presented in OLE Table 14.1.5.2 for the Safety population.

## Efficacy

### ***Primary efficacy analysis***

The primary efficacy endpoint was the difference in the proportion of subjects who achieved EASI-75 at Week 14 (i.e., 2 weeks following the last dose in the double-blind period of the study).

Overall, in the mITT population, 23.0% of subjects in the lirentelimab group were considered EASI-75 responders at Week 14 compared with 18.0% of subjects in the placebo group (Table 1). The proportion of EASI-75 responders in the lirentelimab group was not significantly different than in the placebo group (risk difference versus placebo of 5.1 [95% CI: -9.8, 19.8],  $p=0.4662$ ).

**Table 1 EASI-75 Responder at Week 14 Primary Analysis (mITT Population)**

	<b>Lirentelimab (N=61)</b>	<b>Placebo (N=61)</b>
Week 14 EASI-75 responders	14 (23.0)	11 (18.0)
Week 14 EASI-75 non-responders	47 (77.0)	50 (82.0)
95% CI <sup>a</sup>	13.2, 35.5	9.4, 30.0
Risk difference vs placebo	5.1	

**Table 1 EASI-75 Responder at Week 14 Primary Analysis (mITT Population)**

	<b>Liretelimab (N=61)</b>	<b>Placebo (N=61)</b>
95% CI for risk difference <sup>b</sup>	-9.8, 19.8	
p-value <sup>c</sup>	0.4662	

CI=confidence interval; EASI-75=Eczema Area and Severity Index responders with at least 75% improvement; IGA=Investigator’s Global Assessment; mITT=modified Intent-to-Treat; USA=United States of America.

Note: A Week 14 responder is defined as a 75% improvement from baseline in EASI score at Week 14. Subjects with missing Week 14 EASI score are considered non-responders.

a 95% CI for the binomial EASI response.

b Newcombe common risk difference and 95% confidence limits.

c p-values are derived from the Cochran-Mantel-Haenszel (CMH) 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.

Source: Table 14.2.1.1a.

Supportive analysis in the PP population (risk difference versus placebo of 4.9 [95% CI: -11.7, 21.2], p=0.5376 [Table 14.2.1.1b]) and sensitivity analysis using all subject data (risk difference versus placebo of 6.0 [95% CI: -9.0, 20.6], p=0.3898 [Table 14.2.1.1c]) were not statistically significant.

Subgroup analyses of EASI-75 responders at Week 14 were performed by gender (Table 14.2.1.2.1), age and age at disease onset (Table 14.2.1.2.2 and Table 14.2.1.2.7, respectively), race: White vs non-White and Black vs non-Black (Table 14.2.1.2.3 and Table 14.2.1.2.14, respectively), country (Table 14.2.1.2.5), baseline disease severity index (Table 14.2.1.2.8), baseline EASI severity index (Table 14.2.1.2.9), baseline ppNRS (Table 14.2.1.2.10), specialty vs non-specialty investigators (Table 14.2.1.2.13), percent change in BSA from screening to baseline (Table 14.2.1.2.15), and site (Table 14.2.1.2.16).

Analysis of efficacy response in the Safety population during the OLE period showed that the majority of subjects (48 [63.2%]) compared with AK002-018 baseline and close to a half of subjects (37 [48.7%]) compared with OLE baseline were EASI-75 responders at OLE Week 14. At OLE Week 14 from AK002-018 baseline, 25 (61.0%) subjects in the placebo rollover group and 23 (65.7%) subjects in the lirtelimumab continuing group were EASI-75 responders. While 18 (43.9%) subjects in the placebo rollover group and 19 (54.3%) subjects in the lirtelimumab continuing group were EASI-75 responders at OLE Week 14 from OLE baseline, about half of subjects 39 (51.3%) (23 [56.1%] subjects in the placebo rollover group and 16 [45.7%] subjects in the lirtelimumab continuing group) were non-responders at OLE Week 14 from OLE baseline (OLE Table 14.2.1).

**Secondary efficacy analysis**

Percent Change in EASI from baseline to Week 14

At Week 14 (Day 99), the least squares mean (LSM) EASI decreased from baseline by 36.0% in the lirtelimumab group and by 26.3% in the placebo group (Table 2). The mean reduction from baseline in EASI at Week 14 in the lirtelimumab group was not significantly different than mean reduction in the placebo group (p=0.3968).

**Table 2 Percent Change from Baseline to Week 14 in EASI (mITT Population)**

	<b>Liretelimab (N=61)</b>	<b>Placebo (N=61)</b>
Baseline		
Number of subjects	61	61
Mean (SD)	27.7 (7.3)	30.4 (10.8)
Median (minimum, maximum)	26.8 (16.0, 62.6)	26.9 (16.2, 67.9)
Day 99		
Number of subjects	43	40
Mean (SD)	15.1 (12.8)	19.8 (16.7)
Median (minimum, maximum)	12.3 (0.0, 49.0)	15.5 (0.2, 63.1)
Day 99, percent change from baseline		
Number of subjects	43	40
Mean (SD)	-44.1 (43.6)	-31.3 (62.1)
Median (minimum, maximum)	-52.0 (-100, 49.1)	-50.7 (-99.2, 207)
LSM <sup>a</sup>	-36.0	-26.3
SE of LSM	8.7	8.7
95% CI	-53.1, -18.8	-43.5, -9.1
LSM difference from placebo <sup>a</sup>	-9.7	
SE of LSM <sup>a</sup>	11.4	
95% CI <sup>a</sup>	-32.2, 12.9	
p-value <sup>a</sup>	0.3968	

CI=confidence interval; EASI=Eczema Area and Severity Index; LSM=least squares mean; mITT=modified Intent-to-Treat; SD=standard deviation; SE=standard error.

Note: Only subjects who have a baseline assessment were included.

<sup>a</sup> Based on a mixed model for repeated measures (MMRM) including 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 allowing for random subject effects.

An unstructured covariance matrix is used to model the within subject variance and the Kenward-Rodger's method is used to derive the denominator degrees of freedom.

Source: Table 14.2.2.1a.

At Week 14 (Day 99), in the PP population, the LSM EASI decreased from baseline by 37.2% in the lirtelimumab group and by 25.2% in the placebo group (Table 3). The mean reduction from baseline in EASI at Week 14 in the lirtelimumab group was not significantly different from the mean reduction in the placebo group (p=0.2943).

**Table 3 Percent Change from Baseline to Week 14 in EASI (PP Population)**

	<b>Liretelimab (N=53)</b>	<b>Placebo (N=54)</b>
Baseline		
Number of subjects	53	54
Mean (SD)	26.8 (5.6)	29.5 (9.4)
Median (minimum, maximum)	26.7 (16.0, 40.8)	26.9 (16.2, 56.4)
Day 99		
Number of subjects	43	40
Mean (SD)	15.1 (12.8)	19.8 (16.7)
Median (minimum, maximum)	12.3 (0.0, 49.0)	15.5 (0.2, 63.1)
Day 99, percent change from baseline		
Number of subjects	43	40
Mean (SD)	-44.1 (43.6)	-31.3 (62.1)
Median (minimum, maximum)	-52.0 (-100, 49.1)	-50.7 (-99.2, 207)
LSM <sup>a</sup>	-37.2	-25.2
SE of LSM	9.1	9.1
95% CI	-55.2, -19.3	-43.1, -7.3
LSM difference from placebo <sup>a</sup>	-12.1	
SE of LSM <sup>a</sup>	11.4	
95% CI <sup>a</sup>	(-34.8, 10.6)	
p-value <sup>a</sup>	0.2943	

CI=confidence interval; EASI=Eczema Area and Severity Index; LSM=least squares mean; PP=Per Protocol; SD=standard deviation; SE=standard error.

Note: Only subjects who have a baseline assessment were included.

<sup>a</sup> Based on a mixed model for repeated measures (MMRM) including 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 allowing for random subject effects.

An unstructured covariance matrix is used to model the within subject variance and the Kenward-Rodger's method is used to derive the denominator degrees of freedom.

Source: Table 14.2.2.1b.

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

At Week 14, the proportion of subjects in the mITT population achieving a 1- or 2-point improvement in IGA was 11.5% in the lirtelimumab group and 8.2% in the placebo group (Table 14.2.3a). The proportion of subjects achieving a 1- or 2-point improvement in IGA in the lirtelimumab group was not significantly different than in the placebo group (p=0.7625).

In the PP population, the proportion of subjects achieving a 1- or 2-point improvement in IGA at Week 14 was 13.2% in the lirtelimumab group and 9.3% in the placebo group (Table 14.2.3b). The proportion of subjects achieving a 1- or 2-point improvement in IGA in the PP population Week 14 in the lirtelimumab group was not significantly different than in the placebo group (p=0.5558).

*Change from baseline in absolute peripheral blood counts on eosinophils*

In the mITT population, the mean percent change from baseline was -86.3% and 27.8% for absolute peripheral blood eosinophils at 1 hour after SC dosing in the lirtelimumab and placebo-treated groups, respectively (Table 14.2.7). The depletion in the lirtelimumab-treated group persisted for 24 weeks.

**Eosinophil levels**

Consistent with previously reported antibody-dependent cellular cytotoxicity activity of lirtelimumab on eosinophils, subjects treated with lirtelimumab showed sustained depletion of blood eosinophil counts. In the Safety population, blood eosinophils of lirtelimumab-treated subjects decreased by 86.2% versus blood eosinophils of placebo-treated subjects, which increased by 27.6% on Day 1 post injection during the double-blind period. Decrease in eosinophils in the lirtelimumab group persisted throughout the duration of the double-blind period of the study (Table 14.3.2.1).

Depletion of absolute peripheral blood eosinophil counts was sustained during the OLE period. From AK002-018 baseline in the Safety population, absolute peripheral blood counts of eosinophils decreased by 83.7% overall on OLE Day 1 post injection (77.8% for subjects in the placebo rollover group and 89.5% for subjects in the lirtelimumab continuing group) and by 90.5% overall on OLE Day 99 (89.7% for subjects in the placebo rollover group and 91.5% for subjects in the lirtelimumab continuing group; OLE Table 14.2.2). From OLE baseline in the Safety population, absolute peripheral blood counts of eosinophils decreased by 62.3% overall on OLE Day 1 post injection (82.4% for subjects in the placebo rollover group and 30.1% for subjects in the lirtelimumab continuing group) and by 58.3% overall on OLE Day 99 (89.8% for subjects in the placebo rollover group and 7.6% for subjects in the lirtelimumab continuing group; OLE Table 14.2.2).

In the 2 subjects, whose absolute eosinophil counts was monitored in the extended safety follow-up, the lower absolute eosinophil counts were not considered clinically significant by the investigator. These 2 subjects completed the study at OLE Day 225.

Safety

***Extent of Exposure and Compliance***

The majority of subjects (115 [88.5%] subjects overall, 57 [87.7%] subjects in the lirtelimumab group and 58 [89.2%] subjects in the placebo group) received 7 doses of study drug during the double-blind period of the study (Table 14.1.7.1). The mean and median duration of exposure were 78.8 and 85.0 days, respectively (range: 1 to 106 days). Overall mean treatment compliance was 91.8% (range: 14.3% to 100.0%; Table 14.1.7.3).

A summary of study drug administration during the double-blind period is presented in Table 14.1.7.2.

In the OLE period, 79 (70.5%) subjects overall (42 subjects in the placebo rollover group and 37 subjects in the lirtelimumab continuing group) received 7 doses of study drug (OLE Table 14.1.4.1). Overall, the mean and median duration of exposure were 72.5 and 85.0 days, respectively (range: 1.0 to 99.0 days), and the mean treatment compliance was 85.5% (range: 14.3% to 100.0%; OLE Table 14.1.4.2).

### ***Adverse events***

#### Double-blind period

In the Safety population, all 130 subjects received at least 1 dose of the study drug and majority (115 [88.5%] subjects) completed the study (Table 14.1.1c).

A total of 74 (56.9%) subjects, 35 (53.8%) subjects in the lirentelimab group and 39 (60.0%) subjects in the placebo group, experienced at least 1 TEAE (Table 4). Serious TEAEs were infrequent overall and occurred in a modestly higher proportion of subjects in placebo group than in the lirentelimab group. TEAEs considered by the investigator as related to study drug, TEAEs that led to study drug discontinuation, and TEAESIs were more frequently reported in the lirentelimab group than in the placebo group. There were no deaths during the study.

**Table 4 Overview of Treatment-Emergent Adverse Events (Safety Population)**

<b>Number of Subjects With At Least 1 TEAE Category, %</b>	<b>Lirentelimab (N=65)</b>	<b>Placebo (N=65)</b>	<b>Total (N=130)</b>
TEAE <sup>a</sup>	35 (53.8)	39 (60.0)	74 (56.9)
Treatment-related TEAE	16 (24.6)	11 (16.9)	27 (20.8)
Serious TEAE <sup>b</sup>	1 (1.5)	3 (4.6)	4 (3.1)
Treatment-related serious TEAE <sup>b</sup>	1 (1.5)	0	1 (0.8)
TEAE leading to treatment discontinuation	4 (6.2)	3 (4.6)	7 (5.4)
TEAE leading to study discontinuation	0	0	0
TEAE of special interest <sup>c</sup>	12 (18.5)	4 (6.2)	16 (12.3)
TEAE leading to death	0	0	0

<sup>a</sup> TEAEs are AEs occurring with a date of onset (or worsening) on or after the start date of the of the first SC injection of the study medication.

<sup>b</sup> Serious TEAE are serious AEs occurring with a date of onset (or worsening) on or after the start date of the first SC injection of the study medication.

<sup>c</sup> TEAESI are TEAEs of special interest.

Source: Table 14.3.1.1.

The most common TEAEs (ie, TEAEs reported in  $\geq 5\%$  of subjects by PT in any treatment group during the study) are shown in Table 5. The most frequently reported TEAEs ( $\geq 10\%$  of subjects in any treatment group) were dermatitis atopic (11 [16.9%] subjects in the lirentelimab group and 9 [13.8%] subjects in the placebo group) and injection related reaction (12 [18.5%] subjects in the lirentelimab group and 4 [6.2%] subjects in the placebo group). The number of events of dermatitis atopic and injection related reaction was slightly higher in the lirentelimab group (12 and 13 events, respectively) compared with the placebo group (9 and 6 events, respectively).

The TEAEs of blood creatine phosphokinase increased and upper respiratory tract infection were reported in 5 (7.7%) subjects each in the placebo group only (5 and 6 events, respectively). The TEAEs of headache and nasopharyngitis occurred in similar proportions of subjects and similar numbers of events in both treatment groups.

All other TEAEs were reported in  $< 5\%$  of subjects in any treatment group (Table 14.3.1.2).

**Table 5 Most Common TEAEs Occurring in at Least 5% of Subjects by Preferred Term in Any Treatment Group (Safety Population)**

System Organ Class Preferred Term	Lirentelimab (N=65)		Placebo (N=65)	
	Subjects, n (%)	Events	Subjects, n (%)	Events
At least 1 TEAE	35 (53.8)	85	39 (60.0)	140
<b>Skin and subcutaneous tissue disorders</b>				
Dermatitis atopic	11 (16.9)	12	9 (13.8)	9
<b>Injury, poisoning and procedural complications</b>				
Injection related reaction	12 (18.5)	13	4 (6.2)	6
<b>Nervous system disorders</b>				
Headache	5 (7.7)	6	6 (9.2)	7
<b>Infections and infestations</b>				
Nasopharyngitis	3 (4.6)	3	4 (6.2)	4
Upper respiratory tract infection	0	0	5 (7.7)	6
<b>Investigations</b>				
Blood creatine phosphokinase increased	0	0	5 (7.7)	5

MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.

Note: Adverse events are coded using MedDRA v21.0.

Source: Table 14.3.1.3.

A total of 4 (3.1%) subjects had a serious TEAE, and a modestly higher proportion of subjects in the placebo group (3 [4.6%] subjects) had a serious TEAE compared with the lirentelimab group (1 [1.5%] subject; Table 14.3.1.7). The serious TEAEs in the placebo group were femur fracture (2 subjects) and pulmonary embolism (1 subject); and the serious TEAE in the lirentelimab group was eczema herpeticum (1 subject). The serious TEAE of eczema herpeticum was considered treatment related by the investigator; however, the Medical Monitor considered the event to be anticipated and unlikely to be related to treatment; thus, it did not meet expedited reporting requirements (Table 4, and Listing 16.2.3.1.2). The subject with the serious TEAE of eczema herpeticum discontinued from treatment due to the nonserious TEAE of erysipelas.

Brief summaries of the serious TEAEs are provided below:

- Subject in the lirentelimab group was hospitalized on Day 16 for a serious TEAE of eczema herpeticum. Relevant medical history included dermatitis for the past 28 years. The subject also had a nonserious TEAE of erysipelas from Day 11 to Day 16 that led to discontinuation of study drug. The serious TEAE of eczema herpeticum was considered by the investigator as severe and related to study drug and was resolved on Day 21 following treatment with acyclovir, ampicillin/sulbactam, and topical gentamicin sulfate. As noted above, the Medical Monitor considered the event as unlikely to be related to treatment.
- Subject in the placebo group was hospitalized on Day 99 for a serious TEAE of pulmonary embolism. Relevant medical history included asthma for the past 19 years and allergic rhinitis for the past 15 years. The subject also had nonserious mild TEAEs of

cough and wheezing starting approximately 1 month after 1<sup>st</sup> dose and continuing to Day 112 and a nonserious moderate TEAE of asthma from Day 84 to Day 102. The serious TEAE of pulmonary embolism was considered by the investigator as severe and not related to study drug and was recovering at the time of the database lock date.

- Subject in the placebo group was involved in a motor vehicle accident and was hospitalized on Day 41 for a serious TEAE of femur fracture that was considered by the investigator as severe and not related to study drug. The subject underwent 2 surgeries to insert a rod into the right knee and right femur followed by physical therapy. Additional treatment for the event included acetaminophen. No action was taken with the study drug as a result of the event. The subject was discharged from the hospital on Day 50 and the event was considered resolved.
- Subject in the placebo group fell 9-10 steps from a staircase after “losing his footing” and was hospitalized on Day 12 for a serious TEAE of femur fracture (described as a closed displaced comminuted fracture of the shaft of the right femur) that was considered by the investigator as severe and not related to study drug. The subject underwent surgery to insert a rod into the right femur. Additional treatment for the event included acetaminophen, hydrocodone bitartrate/acetaminophen, and hydromorphone hydrochloride. Study drug was discontinued as a result of the event and the subject discontinued the study. The subject was discharged from the hospital on Day 19 and the event was considered resolved.

Overall, majority of the TEAEs were of moderate severity, with a higher incidence in the placebo group (28 [43.1%] subjects) than in the lirentelimab group (20 [30.8%] subjects; Table 14.3.1.4).

A total of 12 (9.2%) subjects experienced severe TEAEs. The incidence of severe TEAEs was similar between treatment groups (6 [9.2%] subjects each in the lirentelimab and placebo groups; Table 14.3.1.4). Severe TEAEs reported in 2 subjects overall were dermatitis atopic (1 subject each in the lirentelimab and placebo groups), dermatitis (2 subjects in the placebo group), and femur fracture (2 subjects in the placebo group). All other severe TEAEs were each reported in 1 subject overall, which included PTs of hypersensitivity, cellulitis, eczema herpeticum, erysipelas, otitis externa, alanine aminotransferase increased, aspartate aminotransferase increased, and hypertension in 1 subject each in the lirentelimab group and pulmonary embolism in 1 subject in the placebo group.

All events of injection related reaction (12 [18.5%] subjects in the lirentelimab group and 4 [6.2%] subjects in the placebo group) were considered by the investigator as related to study drug and were the most frequently reported treatment-related TEAE in both treatment groups (Table 14.3.1.5). Other treatment-related TEAEs reported in 2 subjects overall were dermatitis atopic (2 subjects in the lirentelimab group), thrombocytosis (1 subject each in the lirentelimab and placebo groups), and headache (1 subject each in the lirentelimab and placebo groups). All other treatment-related TEAEs were reported in 1 subject each in any treatment group.

Four (6.2%) subjects in the lirentelimab group and 3 (4.6%) subjects in the placebo group experienced TEAEs that led to study drug discontinuation (Table 14.3.1.6). The events included dermatitis atopic in 2 subjects in the lirentelimab group; erysipelas and injection related reaction in 1 subject each in the lirentelimab group; hepatomegaly, femur fracture, and acute kidney injury in 1 subject in the placebo group; and thrombocytopenia, hepatomegaly, and blastocystis

infection in 1 subject each in the placebo group (Listing 16.2.3.1.4). All subjects with TEAEs that led to study drug discontinuation have recovered except for 1 subject with dermatitis atopic in the lirentelimab group and 1 subject with blastocystis infection in the placebo group.

A total of 16 (12.3%) subjects experienced a total of 20 TEAESIs (Table 14.3.1.8). All 19 events were injection related reaction (12 subjects with 13 events in the lirentelimab group and 4 subjects with 6 events in the placebo group) except for 1 event of blastocystis infection (1 subject in the placebo group).

#### OLE period

Safety findings in the OLE period were generally consistent with the safety findings during the double-blind period. A total of 61 (54.5%) subjects, 31 (54.4%) subjects in the placebo rollover group and 30 (54.5%) subjects in the lirentelimab continuing group, experienced at least 1 TEAE (OLE Table 14.3.1.1). The overall incidence of TEAEs, serious TEAEs, treatment-related TEAEs, TEAEs leading to discontinuation, and TEAESIs in the OLE period was consistent with those observed in the double-blind period. No deaths were reported in the OLE period.

The most frequently reported TEAEs were injection related reaction (9 [8.0%] subjects overall, all in the placebo rollover group) and nasopharyngitis (9 [8.0%] subjects overall, 4 subjects in the placebo rollover group and 5 subjects in the lirentelimab continuing group). Other common TEAEs were dermatitis atopic (7 [6.3%] subjects overall, 1 subject in the placebo rollover group and 6 subjects in the lirentelimab continuing group), headache (6 [5.4%] subjects overall, 3 subjects each in the placebo rollover and lirentelimab continuing groups), and injection site reaction (6 [5.4%] subjects overall, all in the placebo rollover group; OLE Table 14.3.1.2). The number of events of dermatitis atopic was higher in the lirentelimab continuing group (6 events) compared with the placebo rollover group (1 event); whereas the number of events of injection related reaction and injection site reaction was reported only in the placebo rollover group (11 and 7 events, respectively; OLE Table 14.3.1.3).

All other TEAEs were reported in <5% of subjects in any treatment group (OLE Table 14.3.1.2).

Consistent with the double-blind period, serious TEAEs remained infrequent during the OLE period (2 [1.8%] subjects overall; OLE Table 14.3.1.8). All serious TEAEs (appendicitis and chest pain) were reported in 1 subject each in the lirentelimab continuing group, were considered not related or unlikely related to study drug, and resolved after 3 days (OLE Listing 16.2.3.1.2). The serious TEAE of appendicitis also led to the discontinuation of study drug.

Brief summaries of the serious TEAEs are provided below:

- Subject in the lirentelimab continuing group was hospitalized on Day 75 for a serious TEAE of acute appendicitis, which was considered moderate by the investigator and not related to study drug. Subject was discharged on Day 77 and the event was considered resolved. Due to this serious TEAE, the subject discontinued the study drug and then discontinued the study on Day 114.
- Subject in the lirentelimab continuing group was hospitalized on Day 84 for a serious TEAE of chest pain, which was considered severe by the investigator and unlikely related to study drug. Subject was discharged on Day 86 and recovered fully.

The majority of TEAEs were mild (16 [14.3%] subjects) or moderate (36 [32.1%] subjects) in severity (OLE Table 14.3.1.4). Severe TEAEs occurred in 9 (8.0%) subjects overall (2 subjects

in the placebo rollover group and 7 subjects in the lirentelimab continuing group) and were each reported in 1 subject only, which included herpes virus infection and back pain in the placebo rollover group and motion sickness, chest pain, anaphylactic reaction, hordeolum, nasopharyngitis, alanine aminotransferase increased, aspartate aminotransferase increased, glucose tolerance impaired, dermatitis atopic, and neurodermatitis in the lirentelimab continuing group. No subjects experienced a TEAE considered to be life-threatening by the investigator and no deaths occurred.

TEAEs considered by the investigator as related to study drug were more frequent in subjects in the placebo rollover group (13 [22.8%] subjects) than in the lirentelimab continuing group (3 [5.5%] subjects). This was driven by the TEAEs of injection related reaction and injection site reaction, which were considered by the investigator as related to study drug in 9 and 4 subjects, respectively, in the placebo rollover group versus none of the subjects in the lirentelimab continuing group (OLE Table 14.3.1.5). Other treatment-related TEAE reported in 2 subjects overall was headache (1 subject each in the placebo rollover and lirentelimab continuing groups); all other treatment-related TEAEs were reported in 1 subject each in any treatment group.

Three (2.7%) subjects experienced TEAEs that led to study drug discontinuation (OLE Table 14.3.1.6). The events included injection site reaction in 1 subject in the placebo rollover group, appendicitis and pelvic fluid collection drainage in 1 subject in the lirentelimab continuing group, and alanine aminotransferase increased and aspartate aminotransferase increased in 1 subject in the lirentelimab continuing group (OLE Listing 16.2.3.1.4 and OLE Table 14.3.1.7). All subjects with TEAEs that led to study drug discontinuation have recovered.

A total of 8 (7.1%) subjects experienced a total of 10 TEAESIs (OLE Table 14.3.1.9). All 10 events were injection related reaction in the placebo rollover group and have resolved (OLE Listing 16.2.3.1.5).

### ***Clinical laboratory assessments***

For the majority of hematology and blood chemistry parameters, changes over time in mean values were small and not considered clinically meaningful in either treatment group. For the majority of laboratory parameters, shifts were generally infrequent, with no consistent pattern over time or differences in either treatment group (Table 14.3.2.3 and Table 14.3.2.4, respectively).

There were no clinically meaningful changes in mean values over time in either treatment group in urinalysis parameters (Table 14.3.2.5).

In the OLE period, the OLE baseline is defined as the last test on or prior to the first dose of study drug administration during the OLE. Changes from OLE baseline over time in hematology, blood chemistry, and urinalysis parameters in the OLE period were generally consistent with those observed during the double-blind period of the study (OLE Table 14.3.2.1 through OLE Table 14.3.2.5).

### ***Vital signs, physical findings, and other observations related to safety***

Changes from OLE baseline over time in vital signs in the OLE period were generally consistent with those observed during the double-blind period of the study (OLE Table 14.3.3).

### ***Anti-drug Antibodies***

The following definitions were used to describe subjects positive for ADA ([Shankar 2014](#)).

- **ADA prevalence:** The proportion of all individuals having drug-reactive antibodies (including pre-existing antibodies) at any point in time.
- **Treatment-induced ADA:** Formation of ADA any time after the initial drug administration in a subject without pre-existing ADA.
- **Treatment-boosted ADA:** Pre-existing ADA that were boosted to a higher level following biologic drug administration (any time after the initial drug administration when the ADA titer is greater than or equal to 4-fold of the baseline titer).
- **ADA incidence (treatment-emergent ADA):** The sum of both treatment-induced and treatment-boosted ADA-positive subjects as a proportion of the evaluable subject population.

### Double-Blind period

In Study AK002-018, 131 subjects enrolled in the Safety population and 130 were tested for the presence of serum ADAs. As seen in [Table 6](#), 30 (23.1%) subjects of the 130 tested for ADAs, 13 (20.0%) subjects in the lirentelimab group and 17 (26.2%) subjects in the placebo group, were confirmed positive for ADA at any timepoint.

**Table 6 AK002-018 Double-Blind Period ADAs (Safety Population)**

ADA Category	Lirentelimab n/N (%)	Placebo n/N (%)
Prevalence: Positive at any visit (pre- and post-dose) <sup>1</sup>	13/65 (20%)	17/65 (26.2%)
Only pre-dose positive	9/65 (13.8%)	1/65 (1.5%)
Both pre- and post-dose positive	4/65 (6.2%)	9/65 (13.8%)
Only post-dose positive (treatment-induced)	0/65 (0%)	7/65 (10.8%)
Boosted pre-existing titers (treatment-boosted) (titer $\geq$ 4-fold)	1/65 (1.5%)	3/65 (4.6%)
Incidence: treatment-induced or treatment-boosted	1/65 (1.5%)	10/65 (15.4%)

<sup>1</sup> Predose is defined as Day 1 Baseline in the double-blind period  
Source: Listing 16.2.3.9

In the lirentelimab group, 9 (13.8%) subjects were only positive for ADAs at the predose timepoint. A total of 4 (6.2%) subjects exhibited ADAs at both pre- and postdose timepoints, and 1 (1.5%) subject exhibited treatment boosted ADA titers (i.e., postdose titer was at least 4-fold the predose titer). No subject was categorized as having treatment-induced ADAs (i.e., only postdose positive). No subject in the lirentelimab group exhibited a positive titer at the last visit of the double-blind period (Listing 16.2.3.9).

In the placebo group, 1 (1.5%) subject was only predose positive for ADAs, 9 (13.8%) subjects were positive for ADAs at both pre-and postdose timepoints, and 3 (4.6%) subjects exhibited treatment boosted ADAs. A total of 7 (10.8%) subjects were considered to have treatment-induced ADAs ([Table 6](#)). Only 1 subject was positive for ADAs at the last visit in the double-blind period; however, the last visit titer for this subject was  $\leq$ 32 (Listing 16.2.3.9).

Of the 4 subjects who experienced a SAE during the double-blind portion of Study AK002-018 (Listing 16.2.3.1.2), no subject with an SAE was positive for ADAs at any timepoint. Of the 16 subjects that experienced a TEAESI during the double-blind period (Listing 16.2.3.1.5), 12 subjects were in the lirentelimab group and 4 subjects were in the placebo group. A total of 3 (25.0%) of the subjects experiencing an IRR in the lirentelimab group tested positive for ADAs during the double-blind period. All 3 subjects experienced a single mild IRR event and recovered. Two (50.0%) of the 4 subjects with IRRs in the placebo group, experienced 3 IRR events. All 3 IRR events were mild and the subjects recovered; 1 subject later discontinued the study due to a blastocystic parasitic infection. The overall ADA incidence was higher in the placebo (15.4%) than in the lirentelimab (1.5%) group during the double-blind period.

#### OLE Period

A total of 113 subjects entered the OLE portion of the study, and 112 subjects received study drug and were in the Safety population. For the enrolled subjects, 110 (97.3%) subjects, 54 subjects in the lirentelimab group and 56 subjects in the placebo rollover group, were tested for ADAs. As seen in Table 7, a total of 26 subjects (23.6%), 10 (18.5%) subjects in the lirentelimab and 16 (28.6%) subjects in the placebo rollover group, were confirmed positive for ADAs at any timepoint during the OLE period.

**Table 7 AK002-018 OLE Period ADAs (Safety Population)**

ADA Category	Lirentelimab continuing n/N (%)	Placebo rollover n/N (%)
Prevalence: Positive at any visit (pre- and post-dose) <sup>1</sup>	10/54 (18.5%)	16/56 (28.6%)
Only pre-dose positive	0/54 (0%)	8/56 (14.3%)
Both pre- and post-dose positive	4/54 (7.4%)	1/56 (1.8%)
Only post-dose positive (treatment-induced)	6/54 (11.1%)	7/56 (12.5%)
Boosted pre-existing titers (treatment-boostered) (titer ≥4-fold)	1/54 (1.9%)	0/56 (0%)
Incidence: treatment-induced or treatment-boostered	7/54 (13%)	7/56 (12.5%)

<sup>1</sup> Predose is defined as before the 1<sup>st</sup> dose of OLE period or before the last visit of the double-blind period on Day 85.

Source: OLE Listing 16.2.3.8

In the lirentelimab group, 4 (7.4%) subjects were both pre- and postdose positive for ADAs, with 1 (1.9%) subject exhibiting treatment-boostered ADAs. There were 6 (11.1%) subjects that were only postdose positive for ADAs and categorized as having treatment-induced ADAs. The overall incidence of ADA-positive subjects was similar in the lirentelimab continuing group as in the placebo rollover group during the OLE period.

In the placebo rollover group, 8 (14.3%) subjects were only predose positive in the OLE period. Only 1 (1.8%) subject was both pre-and postdose positive and no subject was categorized as having treatment-boostered post-dose ADA titers. The overall incidence of ADA-positive subjects

in the placebo rollover group, 7 (12.5%), was composed totally of subjects designated as treatment-induced.

In total, 18 subjects were positive for ADAs at the last OLE period visit, 15 with a last visit titer  $\leq 32$  and 3 subjects with a last visit titer  $\geq 64$  (Listing 16.2.3.8)

Of the 2 subjects who experienced a SAE during the OLE portion of Study AK002-018, no subject with an SAE was positive for ADAs at any timepoint. A total of 8 subjects, all in the placebo rollover group, experienced a total of 10 IRRs (OLE Listing 16.2.3.1.5). None of the 8 subjects that experienced a TEAESI of IRR during OLE period tested positive for ADAs.

In summary, there was no indication of an effect of ADA-positive status on safety in Study AK002-018. Based on available information, there was no apparent relationship between ADA response and either the frequency or severity of SAEs or IRRs during Study AK002-018; however, due to the low number of subjects positive for ADAs observed in the study, the effect of immunogenicity on the safety of lirentelimab is unknown.

## Conclusions

The purpose of this study was to test the hypothesis that lirentelimab was different from placebo with regards to the primary efficacy endpoint of the proportion of subjects who achieved at least 75% improvement from baseline in EASI at Week 14.

Overall, treatment with lirentelimab improved EASI by 75% in more subjects than treatment with placebo at Week 14 of the double-blind period of the study (23.0% vs 18.0%). However, the proportion of EASI-75 responders from baseline to Week 14 was not significantly different than in the placebo group. Because a significantly greater proportion of EASI-75 responders in the lirentelimab group compared to placebo was required to meet the primary endpoint, this study did not meet its primary efficacy endpoint. A similar pattern was observed in the PP population and in the sensitivity analysis using all subject data. Results from the secondary efficacy endpoints of percent change in EASI from baseline to Week 14 and the proportion of subjects achieving a 1- or 2-point improvement in IGA in the lirentelimab group were also not significantly different from placebo.

As expected from its mechanism of action, lirentelimab treatment resulted in a rapid and sustained depletion of eosinophils from the peripheral circulation.

Overall, lirentelimab was well tolerated in adults with AD for up to 14 doses and up to 300 mg administered every 2 weeks during the double-blind and OLE periods of the study. A total of 74 (56.9%) subjects, 35 (53.8%) subjects in the lirentelimab group and 39 (60.0%) subjects in the placebo group, experienced at least 1 TEAE during the double-blind period.

Four (3.1%) subjects (1 subject in the lirentelimab group and 3 subjects in the placebo group) experienced serious TEAEs, with the serious TEAE in the subject in the lirentelimab group considered by the investigator to be related to the study drug. Seven (5.4%) subjects (4 subjects in the lirentelimab group and 3 subjects in the placebo group) experienced TEAEs that led to study drug discontinuation. No life-threatening TEAEs or deaths were reported during the study.

The most frequently reported TEAEs ( $\geq 10\%$  of subjects in any treatment group) during the double-blind period were dermatitis atopic (16.9% in the lirentelimab group and 13.8% in the placebo group) and injection related reaction (18.5% in the lirentelimab group and 6.2% in the placebo group). The number of events of both TEAEs was slightly higher in the lirentelimab

group compared with the placebo group. In addition, all events of injection related reaction were considered by the investigator as related to study drug and were the most frequently reported treatment-related TEAE in both treatment groups.

Safety findings in the OLE period were generally consistent with the safety findings during the double-blind period.

No clinically significant abnormalities in hematology, serum chemistry, urinalysis, or vital signs were observed during the double-blind and OLE periods of the study.

No relationship between ADA and safety events was observed; however, due to the low number of subjects positive for ADAs observed in the study, the effect of immunogenicity on the safety of lirentelimab is unknown.

In conclusion, although the proportion of subjects with moderate-to-severe AD inadequately controlled by topical treatments who achieved improvements in EASI-75 score at Week 14 was numerically higher in the lirentelimab group, the placebo-adjusted difference was not statistically significant. Lirentelimab was well tolerated, and safety profile was similar to that reported in previous clinical studies with lirentelimab. The most common TEAEs was injection related reaction. Lirentelimab appeared to be well tolerated in long-term dosing.

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