1 SYNOPSIS

Protocol Number	AK002-027
Title	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Lirentelimab in Adult Subjects with H-1 Antihistamine Refractory Chronic Spontaneous Urticaria
Sponsor	Allakos Inc.
Clinical Trial Registry Identifiers	NCT ID: NCT05528861 EudraCT ID: 2022-001847-26
IND Number	137491
Indication Studied	H-1 Antihistamine Refractory Chronic Spontaneous Urticaria
Investigational Product(s)	Finished Product: Lirentelimab subcutaneous (SC) drug product Active Ingredient: Lirentelimab (AK002) Dose: 300 mg Mode of Administration: SC Batch Number(s): Double-blind period: 000596831, 0000644473 Open-label extension (OLE): 000596831, 0000644473, 0000659229 Duration of Therapy: 6 doses (1 dose every 2 weeks) in the double-blind period of the study 6 doses (1 dose every 2 weeks) in the optional OLE period of the study
Reference Therapy	Finished Product: Placebo SC drug product Active Ingredient: Placebo Dose(s): Not applicable Mode of Administration: SC Batch Number(s): 686452 Duration of Therapy: 6 doses (1 dose every 2 weeks) in the double-blind period of the study
Investigators and Study Centers	67 clinical sites (51 United States [IND 137491], 12 Germany, and 4 Poland)
Phase and Design	2
Conduct Period	Start Date:11 October 2022 Double-blind Period Database Lock Date: 04 January 2024 Stop Date: 27 December 2023 OLE Period Stop Date: 04 June 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: 10 May 2024

Number of Subjects (Planned and Analyzed)	It was anticipated that approximately 130 subjects (65 per dose group) at approximately 70 international investigative sites would be enrolled. The actual number of subjects enrolled was 127 at 67 investigative sites.

Study AK002-027 was terminated early after all subjects completed the double-blind period due to lack of efficacy of lirentelimab 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	Objective(s)	Endpoints
Primary	To characterize the efficacy of lirentelimab SC in omalizumab-naïve and omalizumab-exposed adult subjects with H1-antihistamine (AH) refractory chronic spontaneous urticaria (CSU) when compared to placebo.	Absolute change from baseline in weekly Urticaria Assessment Score (UAS7) at Week 12 The associated estimand for this objective was the effect of therapy with lirentelimab SC as assessed by the absolute change in weekly UAS7 from baseline to Week 12.
Secondary Efficacy	To further characterize the efficacy of lirentelimab SC in adult subjects with H1-AH refractory CSU when compared to placebo.	1. Improvement of severity of hives assessed as absolute change from baseline in weekly Hives Severity Score (HSS7) at Week 12. 2. Improvement of severity of itch assessed as absolute change from baseline in weekly Itch Severity Score (ISS7) at Week 12. 3. Complete absence of hives and itch at Week 12 assessed as proportion of subjects achieving UAS7=0.

Safety Objectives

To evaluate the safety and tolerability of lirentelimab SC in adult subjects with H1-AH refractory CSU by determining incidence and severity of adverse events (AEs), study withdrawals due to AEs, changes in vital signs and laboratory tests including immunogenicity, changes in concomitant medication beginning on or after the first injection of study drug, 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 6 doses of lirentelimab SC in subjects with moderate-to-severe CSU who completed Day 85 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 is a Phase 2, proof-of-concept, multicenter, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of lirentelimab in adult subjects with moderate-to-severe

H1-AH refractory CSU. Subjects enrolled in the study received 6 doses of 300 mg lirentelimab or placebo SC administered every 2 weeks, followed by the optional OLE period. Subjects were observed for a post-treatment period of 12 weeks.

The study was designed as follows:

- A screening period of up to 3 weeks prior to study drug administration. Subjects on a stable, approved dose regimen of 2nd generation or later H1-AH prior to screening underwent a 2-week eligibility screening period or subjects not on a stable approved 2nd generation or later H1-AH dose regimen were allowed an additional 1 week during the screening period to reach a stable approved dosing regimen before entering the 2-week eligibility screening period.
- Stable approved doses of H1-AH for study purposes were defined as a H1-AH regimen between 1× and 4× of the licensed dose and at the licensed frequency of dosing for the treatment of CSU for at least 1 week prior to screening.
- Baseline H1-AH dosing regimen must have been established by Day -14 (14 days prior to randomization) for purposes of the screening eligibility period. Baseline disease activity data were collected with daily assessment of itch and hive severity, both of which were used to calculate UAS7.
- Subjects who met eligibility criteria at both Day -7 and Day 1 were enrolled into the study and stratified at randomization based on omalizumab experience for the treatment of CSU (exposed or naïve) and UAS7 (16–27 or 28–42).
- Eligible subjects received the first dose of lirentelimab SC or placebo SC on Day 1. If the study drug is well tolerated (no stopping rules being met), subjects continued to receive subsequent doses on Days 15, 29, 43, 57, and 71, for a total of 6 doses.
- Subjects remained in the clinic for at least 1 hour of observation (or longer, as per Investigator's discretion) following the end of dose administration after each dose. In the event of an infusion-related reaction, the subject could have required prolonged observation (>1 hour or until the symptoms resolved), as per Investigator's discretion. Subjects were also instructed to immediately contact the study team if any reactions occurred after discharge.
- Subjects were given an option of entering the OLE period to receive 6 additional doses of 300 mg lirentelimab SC, contingent on meeting defined study selection criteria.
- Subjects were followed for 12 weeks after last dose in the randomized double-blind period or OLE period.
- Subjects completed a number of assessments and questionnaires, including Urticaria Patient Daily Diary (UPDD), throughout the duration of the study.
- Total study duration was approximately 6 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 was done on Day 85 of 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 85 visit. The subsequent injections occurred on Days 15, 29, 43, 57, and 71 (±5 days). 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 155/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 211 ±7 days), ~~but~~ 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 211 ±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 with CSU were eligible to enroll in 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 subjects ≥18 years of age at the time of screening.
3. CSU diagnosis for ≥6 months.
4. Diagnosis of moderate-severe CSU refractory to H1-AH at a minimum of the licensed dose at the licensed frequency at the time of randomization as defined by the following:
    - Presence of hives and itch for ≥6 consecutive weeks prior to Screening Visit 1
    - UAS7 (range 0-42) ≥16 and HSS7 (range 0-21) ≥8 during the 7 consecutive days prior to Screening Day -7 Phone Visit and during the 7 consecutive days prior to randomization (Day 1)
5. Subjects who are omalizumab-naïve or omalizumab-exposed. Omalizumab-exposed subjects are those that have demonstrated secondary loss of response, intolerance, or lack of access to biologics due to economic reasons.
6. Subjects must have been on a stable dose of H1-AH, between 1× and 4× of the licensed dose and at the licensed dosing frequency, for treatment of CSU for at least 1 week prior to screening and were willing to remain on a stable dose throughout the study.
7. Able and compliant with completing a daily symptom eDiary for the duration of the study and adherent to the study visit schedules.

Subjects were excluded from the study if they met any of the following criteria:

1. History of hypersensitivity to the study drugs or their excipients or to drugs of similar chemical classes (i.e., murine, chimeric or human antibodies)
2. Current use of biologics for any indication.
3. Demonstrated lack of primary response to treatment with a biologic therapy (e.g., omalizumab) for the treatment of CSU, defined as no response to treatment despite complete adherence to the prescribed regimen (e.g., a stable dose of omalizumab at ≥300 mg per month) for at least 3 months based on interview at screening.
4. 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:

- 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), and eosinophil-depleting drugs (e.g., pramipexole).
- Routine (daily or every other day during 5 or more consecutive days) doses of systemic hydroxychloroquine.
- Plasmapheresis.

5. Used oral Janus kinase inhibitors within 8 weeks of the baseline visit (required discussion with Medical Monitor prior to subject enrollment in the study)
6. Used any of the following treatments within 3 weeks prior to the baseline visit:

   - H2-AH
   - Routine (daily or every other day during 5 or more consecutive days) doses of systemic corticosteroids
   - Regular (daily or every other day) doxepin (oral)
   - Leukotriene receptor antagonists (e.g., montelukast, zafirlukast)

7. Used H1-AH at greater than approved doses or greater than local CSU guideline recommended doses after Screening Visit 1
8. Previous treatment with biologics or intravenous immunoglobulin:

   - 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.
   - Other biologics, including investigational biologics (e.g., dupilumab, omalizumab, benralizumab, etc.) and tumor necrosis factor inhibitors (e.g., infliximab, adalimumab) within 5 half-lives if known or 8 weeks prior to the baseline visit, whichever was longer.
   - Intravenous immunoglobulin within 5 half-lives.

9. Planned or anticipated use of any prohibited medication.
10. Subjects had causes other than CSU for their urticaria, including symptomatic dermographism, cholinergic urticaria, or any inducible urticaria.
11. Diseases other than chronic urticaria with urticarial or angioedema symptoms, including chronic itching, that in the Investigator's opinion might influence study evaluations and results.
12. Subjects with known or suspected urticarial vasculitis.
13. Subjects with known or suspected hereditary angioedema.
14. Any other skin disease associated with chronic itch, including atopic dermatitis, that in the Investigator's opinion might influence study outcome and subject's interpretation of symptoms caused by CSU.
15. 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.
16. Evidence of active HIV infection at screening based on serology or evidence of active hepatitis B or C at screening based on serology.

17. Presence of an abnormal screening laboratory value considered to be clinically significant by the Investigator.
18. 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.
19. Treatment with chemotherapy or radiotherapy in the preceding 6 months.
20. History of malignancy except carcinoma in situ in the cervix, early-stage prostate cancer, or non-melanoma skin cancers.
21. Women who were pregnant, breastfeeding, or planning to become pregnant while participating in the study.
22. 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).
23. Subjects who weighed <40 kg at screening.
24. Any other reason that in the opinion of the Investigator or the Medical Monitor made the subject unsuitable for enrollment.
25. 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 Population

- The **Intent-to-Treat (ITT) population** included all subjects who were randomized to treatment.
- The **Safety population** included all subjects who were randomized and received at least 1 dose of 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 dose 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 inclusion criteria numbers 3, 4, 5, or 6). The mITT population was used for all efficacy analysis.
- The **Per Protocol (PP) population** included subjects in the mITT population who had received all 6 doses of study drug and did not have major protocol violations possibly interfering with the interpretation of efficacy and safety assessments. The PP population was used to evaluate sensitivity of the primary endpoint and secondary endpoints.

Primary Endpoint Analysis

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

H_0: No treatment difference between lirentelimab SC and placebo SC.

H_1: There was a treatment difference between lirentelimab SC and placebo SC.

The primary endpoint was analyzed using analysis of covariance (ANCOVA). The least squares (LS) mean, standard error (SE), and 95% confidence interval (CI) for each treatment group and for the between group difference was derived from the ANCOVA model with treatment as a factor and baseline UAS7 (continuous) and omalizumab experience for the treatment of CSU (exposed versus naïve) as covariates. Data on subjects who experienced an intercurrent event (ICE; i.e., exit the study prematurely or initiate prohibited or rescue medications) prior to the end of Week 12 were set to missing.

Secondary Endpoint Analysis

Binary data were analyzed using the Cochran-Mantel-Haenszel test, stratified by the randomization stratification factors (omalizumab experience for the treatment of CSU [exposed versus naïve] and UAS7 [16–27 versus 28–42]). Data on subjects who experienced an ICE prior to the end of Week 12 were set to non-response status.

All secondary efficacy endpoints of continuous nature utilized mixed model for repeated measures (MMRM) procedure 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. The model included fixed effects for baseline value, randomization stratification factor, treatment, week, the treatment by week interaction, baseline value by week interaction, and allow for random subject effects.

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
- TEAE by system organ class (SOC) and preferred term (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 planned for the double-blind portion of this study.

Changes in the Conduct of the Study or Planned Analyses

Overall, 4 global and 5 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	26 May 2022	Global: USA and Germany
Amendment 1	05 August 2022	Global: USA and Germany
Overall Rationale for the Amendment: The protocol was amended to gather additional data on subjects with CSU who are biologic-naïve and biologic-exposed and to modify screening and enrollment requirements, including prohibited treatments and medications. Key changes included adding text to describe the OLE period, option to participate, and eligibility requirements. Minor text and formatting edits were also made throughout the document for clarity and consistency.		
Amendment 1.1	16 November 2022	Germany only
Overall Rationale for the Amendment: The protocol was amended to satisfy the comments received from Paul Ehrlich Institute, the Federal Institute for Vaccines and Biomedicines in Germany on 03 November 2022. Key changes included adding text to clarify screening and enrollment requirements for treatments and medications, adding a study design diagram, and inserting sections for end of study definition and benefit-risk assessment. Additional references also were added.		
Amendment 1.2	21 November 2022	Germany only
Overall Rationale for the Amendment: The protocol was amended to include changes anticipated to be specifically requested by the Central Ethic Committee in Germany. Key changes included updating the clinical exposure of lirentelimab, adding justification for the study site number, adding exclusion criteria, adding requirements for COVID-19 testing and COVID-19 vaccination, adding study stopping rules, and specifying requirements for the demographics and baseline characteristics collected on the CRF form, the Declaration of Helsinki version, and the allowed reimbursement for study participation for subjects residing in Germany.		
Amendment 1.3	16 February 2023	Germany only
Overall Rationale for the Amendment: Key changes in this amendment included adding a section on rationale for study design, with associated references, and edits to study stopping rules.		

Protocol	Date	Region(s)
Amendment 2	15 December 2022	USA and Poland
Overall Rationale for the Amendment: The protocol was amended to incorporate the clarifications for study conduct as well as the updates specifically requested by the Paul Ehrlich Institute and the Central Ethic Committee in Germany. Key changes in this amendment included adding sites in Poland, updating the benefit-risk section, adding an Atopic Conditions Questionnaire to the assessments, specifying the patient-reported outcome requirements during screening, specifying pregnancy testing requirements, adding optional biopsy collection, and clarifying procedures.		
Amendment 2.1	19 April 2023	Germany only
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, and clarifying assessment procedures. Additional regional changes that may not apply to Germany, such as optional biopsy collection in the US and subject payment restrictions in Poland, were included for the purposes of maintaining complete information.		
Amendment 3	07 September 2023	Global: USA, Germany, and Poland
Overall Rationale for the Amendment: Key changes in this amendment included updated language to reflect the required source documents for study entry, adjusted statistical analysis, clarification of the concomitant H1-AH treatment, and updated description of the investigational products.		
Amendment 4	22 September 2023	USA only
Overall Rationale for the Amendment: The key change in this amendment was an update to the number of subjects to be randomized.		
Amendment 4.1	23 February 2024	Germany and Poland only
Overall Rationale for the Amendment: Key changes in this amendment included an administrative update for medical monitor and an update to the Schedule of Assessments for OLE period regarding length of follow-up after last visit to allow for Investigator assessment of clinical relevance of abnormal laboratory value, and an update to the number of subjects to be randomized.		

Subject Disposition

A total of 127 subjects (66 subjects in the lirentelimab group and 61 subjects in the placebo group) were randomized in Study AK002-027, all of whom received at least 1 dose of the study drug (Table 14.1.1a). The majority of subjects (117 [92.1%] subjects overall, 60 [90.9%] subjects in the lirentelimab group and 57 [93.4%] subjects in the placebo group) completed the double-blind period of the study. Of the 10 subjects (6 subjects in the lirentelimab group and 4 subjects in the placebo group) who discontinued study participation, 4 (3.1%) subjects (2 subjects each in the lirentelimab and placebo groups) withdrew consent, 2 (1.6%) subjects (in the lirentelimab group) were lost to follow up, 1 (0.8%) subject (in the lirentelimab group) discontinued due to an AE, 1 (0.8%) subject (in the placebo group) discontinued due to Sponsor decision, and 2 (1.6%) subjects (1 subject each in the lirentelimab and placebo groups were withdrawn due to other reasons.

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 17 (13.4%) subjects (7 [10.6%] subjects in the lirentelimab group and 10 [16.4%] subjects in the placebo group) had at least 1 major protocol deviation during the double-blind period of the study, which were related to study assessments/study visits (4 subjects each in the lirentelimab and placebo groups), inclusion/exclusion criteria (2 subjects each in the lirentelimab and placebo groups), dose formulation/dose administration/overuse/misuse of investigational product (1 subject in the lirentelimab group and 2 subjects in the placebo group), informed consent (1 subject in the placebo group), and other (1 subject in the placebo group [Table 14.1.2 and Listing 16.2.1.2]).

All 127 randomized subjects were included in the ITT and Safety populations, with 66 subjects in the lirentelimab group and 61 subjects in the placebo group (Table 14.1.3). Subject counts in the various analysis populations are depicted in Table 1. 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.

Table 1 Analysis Population: Subject Count (All Randomized Subjects)

Population	Lirentelimab (N=66) n (%)	Placebo (N=61) n (%)	Total (N=127) n (%)
Randomized/Intent-to-Treat	66 (100)	61 (100)	127 (100)
Safety	66 (100)	61 (100)	127 (100)
Modified Intent-to-Treat	64 (97.0)	59 (96.7)	123 (96.9)
Per Protocol	59 (89.4)	56 (91.8)	115 (90.6)

Source: Table 14.1.3

OLE Period

A total of 118 subjects entered the OLE portion of the study, and 117 subjects received study drug; of these, 57 subjects rolled over from the placebo group and 60 subjects continued lirentelimab treatment from the double-blind period of the study (OLE Table 14.1.1). In the OLE period, subjects received up to additional 6 doses of open-label 300 mg lirentelimab SC. A total of 51 (43.6%) subjects completed the OLE period and 6 (5.1%) subjects at study sites in Germany and Poland 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 211±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. Out of the 6 subjects enrolled in the safety follow-up period 3 subjects completed the study at OLE Day 211. While the lower absolute eosinophil counts were not considered clinically significant by the investigator, the remaining 3 subjects were referred for additional evaluation and follow-up with their treating physician.

Of the 60 (51.3%) subjects who discontinued study participation (27 subjects in the placebo rollover group and 33 subjects in the lirentelimab continuing group), 37 (31.6%) subjects

withdrew due to Sponsor decision, 15 (12.8%) subjects withdrew consent, 4 (3.4%) subjects discontinued due to an AE, 2 (1.7%) subjects were lost to follow-up, 1 (0.9%) subject discontinued due to physician's decision, 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 5 (4.2%) subjects (4 subjects in the placebo rollover group and 1 subject 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 placebo rollover group and 1 subject in the lirentelimab continuing group) and dose formulation/dose administration/overuse/misuse of investigational product (2 subjects 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 in regard to age, ethnicity, race, height, weight, and body mass index (Table 14.1.5a). Overall, the majority of subjects were female (107 [84.3%]), not Hispanic or Latino (107 [84.3%]), and White (97 [76.4%]). The mean age was 44 years (range: 19 to 77 years), and the mean body mass index was 30.3 kg/m^2 (range: 17.9 to 53.7 kg/m^2). 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 (101 [86.3%]), not Hispanic or Latino (99 [84.6%]), and White (91 [77.8%]). The mean age was 45 years (range: 20 to 78 years), and the mean body mass index was 30.7 kg/m^2 (range: 17.6 to 55.3 kg/m^2).

Baseline disease characteristics

Baseline disease characteristics including, but not limited to, ISS7, UAS7, HSS7, Dermatology Life Quality Index total score, and Urticaria Control Test score were collected at study entry (Table 14.1.10a).

Overall, there were no clear differences in baseline disease characteristics between the treatment groups of the Safety population during the double-blind period of the study. The majority of subjects were omalizumab-naïve (87 [68.5%]) and had a UAS7 of 28 to 42 (83 [65.4%]), an ISS7 of at least 13 (97 [76.4%]), and a HSS7 of at least 13 (89 [70.1%]). The mean baseline UAS7 was 31.4 (range: 16.0 to 42.0), the mean baseline ISS7 was 16.1 (range: 0 to 21.0), and the mean baseline HSS7 was 15.3 (range: 7.0 to 21.0).

Baseline disease characteristics of the mITT and PP populations are summarized in Table 14.1.10b and Table 14.1.10c, respectively.

All subjects (100%) had at least 1 medical history condition (Table 14.1.6). The most frequently reported medical history conditions (≥20% of subjects overall) of the Safety population were within the MedDRA SOCs of skin and subcutaneous tissue disorders (100%); respiratory, thoracic and mediastinal disorders (47.2%); surgical and medical procedures (44.9%);

psychiatric disorders (40.2%); gastrointestinal disorders (36.2%); metabolism and nutrition disorders (36.2%); nervous system disorders (33.9%); infections and infestations (32.3%); immune system disorders (31.5%); musculoskeletal and connective tissue disorders (29.9%); social circumstances (23.6%); and vascular disorders (22.8%). By PT, the most frequently reported medical history conditions (≥30% of subjects overall) were angioedema (38.6%), and rhinitis allergic (31.5%).

All subjects (100%) received medications prior to study entry (Table 14.1.8.1a). The most frequently used medications prior to study entry (≥30% of subjects overall) were piperazine derivatives (78.0%), other antihistamines for systemic use (52.8%), glucocorticoids (42.5%), other monoclonal antibodies and antibody drug conjugates (35.4%), and aminoalkyl ethers (33.9%). Prior medication use of the mITT population is summarized in Table 14.1.8.1b.

All subjects (100%) used concomitant medications during the study (Table 14.1.8.2a). The most frequently used concomitant medications (≥20% of subjects overall) were piperazine derivatives (64.6%), other antihistamines for systemic use (37.8%), and selective beta-2-adrenoreceptor agonists (20.5%). Concomitant medication use of the mITT population is summarized in Table 14.1.8.2b.

A total of 52.8% of subjects had newly initiated medications during the study (i.e., medications started after the first dose of study drug; Table 14.1.8.3a). The most frequently reported newly initiated medications (≥5% of subjects overall) were anilides (8.7%) and propionic acid derivatives (7.9%). Newly initiated medications of the mITT population are summarized in Table 14.1.8.3b.

AK002-027 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 absolute change from baseline in UAS7 at Week 12 (i.e., 2 weeks after the last dose in the double-blind period of the study).

In the mITT population, the LS mean change from baseline in UAS7 at Week 12 was -7.9 for subjects in the lirentelimab group and -8.4 for subjects in the placebo group (Table 2). The LS mean difference from baseline in UAS7 at Week 12 in the lirentelimab group was not statistically different from that in the placebo group (difference versus placebo of 0.5 [95% CI: -3.6, 4.5], p=0.8174). Similar results in the LS mean change from baseline in UAS7 at Week 12 were observed in the PP population (difference versus placebo of 0.3 [95% CI: -3.9, 4.4], p=0.8961; Table 14.2.1.1b).

Table 2 Change from Baseline in UAS7 at Week 12 – Primary Analysis (mITT Population)

	Lirentelimab (N=64)	Placebo (N=59)
Baseline		
Number of subjects	64	59
Mean (SD)	31.4 (7.2)	32.4 (7.4)
Median (minimum, maximum)	31.0 (18.0, 42.0)	33.8 (16.0, 42.0)
Week 12		
Number of subjects	56	52
Mean (SD)	22.0 (12.9)	22.3 (12.4)
Median (minimum, maximum)	22.0 (0.0, 42.0)	21.0 (1.0, 42.0)
Week 12, change from baseline		
Mean (SD)	-8.9 (10.5)	-9.9 (11.6)
Median (minimum, maximum)	-7.5 (-39.0, 12.8)	-9.5 (-32.8, 11.7)
LS mean (SE) [a]	-7.9 (1.9)	-8.4 (2.0)
95% CI	(-11.6, -4.2)	(-12.2, -4.5)
LSM difference from placebo (SE) [a]	0.5 (2.1)	
95% CI	(-3.6, 4.5)	
p-value	0.8174	

CI=confidence interval; CSU=chronic spontaneous urticaria; LS=least squares; mITT=modified Intent-to-Treat; SD=standard deviation; SE=standard error; UAS7=weekly Urticaria Assessment Score; U.S.=United States.

[a] Based on analysis of covariance using imputed data with treatment as a factor, and baseline UAS7, omalizumab experience for the treatment of CSU (exposed, naïve), and country (U.S., non-U.S.) as covariates.

Source: Table 14.2.1.1a

Subgroup analyses of change from baseline in UAS7 at Week 12 were performed by sex (Table 14.2.1.2.1), age group (Table 14.2.1.2.2), race (Table 14.2.1.2.3), ethnicity (Table 14.2.1.2.4), region (Table 14.2.1.2.5), baseline ISS7 (Table 14.2.1.2.6), history of angioedema (Table 14.2.1.2.7), prior omalizumab experience for the treatment of CSU (Table 14.2.1.2.8), baseline UAS7 score (Table 14.2.1.2.9), duration of disease prior to baseline (Table 14.2.1.2.10), and screening immunoglobulin E level (Table 14.2.1.2.11).

The change from baseline in UAS7 over time in the mITT and PP populations are provided in Table 14.2.2.1a and Table 14.2.2.1b.

Analysis of efficacy response in the Safety population based on the observed data during the OLE period showed a reduction in the UAS7 measurement of disease activity over time. The mean change from AK002-027 baseline in UAS7 at Week 12 was -12.5 for subjects in the placebo rollover group and -17.9 for subjects in the lirentelimab continuing group; and the mean change from OLE baseline in UAS7 at Week 12 was -3.8 for subjects in the placebo rollover group and -7.5 for subjects in the lirentelimab continuing group. A reduction was also seen in the mean UAS7 score at the OLE baseline (mean 22.1, SD 12.5) compared to AK002-027 baseline (mean 31.5, SD 7.5; OLE Table 14.2.1).

Secondary efficacy analysis

Absolute change from baseline in HSS7 at Week 12

In the mITT population, the LS mean change from baseline in HSS7 at Week 12 was -4.0 for subjects in the lirentelimab group and -4.6 for subjects in the placebo group (Table 3). The LS mean difference from baseline in HSS7 at Week 12 in the lirentelimab group was not statistically different from that in the placebo group (difference versus placebo of 0.6 [95% CI: -1.6, 2.8], p=0.5857). Similar results in the LS mean change from baseline in HSS7 at Week 12 were observed in the PP population (difference versus placebo of 0.4 [95% CI: -1.8, 2.6], p=0.7412; Table 14.2.2.2b).

Table 3 Change from Baseline in HSS7 at Week 12 (mITT Population)

	Lirentelimab (N=64)	**Placebo (N=59)**
Baseline		
Number of subjects	64	59
Mean (SD)	15.1 (4.1)	16.0 (3.9)
Median (minimum, maximum)	14.5 (8.0, 21.0)	17.0 (8.0, 21.0)
Week 12		
Number of subjects	56	52
Mean (SD)	10.6 (6.5)	10.9 (6.7)
Median (minimum, maximum)	9.5 (0.0, 21.0)	8.9 (0.0, 21.0)
Week 12, change from baseline		
Mean (SD)	-4.3 (5.8)	-5.1 (6.0)
Median (minimum, maximum)	-4.5 (-20.0, 7.0)	-5.3 (-17.5, 7.0)
LS mean (SE) [a]	-4.0 (0.8)	-4.6 (0.9)
95% CI	(-5.6, -2.3)	(-6.3, -2.9)
LSM difference from placebo (SE) [a]	0.6 (1.1)	
95% CI	(-1.6, 2.8)	
p-value	0.5857	

CI=confidence interval; CSU=chronic spontaneous urticaria; HSS7=weekly Hives Severity Score; LS=least squares; mITT=modified Intent-to-Treat; SD=standard deviation; SE=standard error; UAS7=weekly Urticaria Assessment Score; U.S.=United States.

[a] Based on a mixed model for repeated measures using data censored without imputation including fixed effects for baseline value, omalizumab experience for the treatment of CSU, UAS7 (16–27, 28–42), country (U.S., non-U.S.), treatment, study week, the treatment-by-week interaction, and the baseline by-week interaction and allowing for random subject effects.

Source: Table 14.2.2.2a

Absolute change from baseline in ISS7 at Week 12

In the mITT population, the LS mean change from baseline in ISS7 at Week 12 was -4.4 for subjects in the lirentelimab group and -4.3 for subjects in the placebo group (Table 4). The LS mean difference from baseline in ISS7 at Week 12 in the lirentelimab group was not statistically different from that in the placebo group (difference versus placebo of -0.1 [95% CI: -2.2, 2.1], p=0.9633). Similar results in the LS mean change from baseline in ISS7 at Week 12 were observed in the PP population (difference versus placebo of -0.1 [95% CI: -2.3, 2.1], p=0.9418; Table 14.2.2.3b).

Table 4 Change from Baseline in ISS7 at Week 12 (mITT Population)

	Lirentelimab (N=64)	**Placebo (N=59)**
Baseline		
Number of subjects	64	59
Mean (SD)	16.3 (4.4)	16.3 (4.2)
Median (minimum, maximum)	17.5 (0.0, 21.0)	17.0 (7.0, 21.0)
Week 12		
Number of subjects	56	52
Mean (SD)	11.4 (6.8)	11.5 (6.4)
Median (minimum, maximum)	13.5 (0.0, 21.0)	12.4 (0.0, 21.0)
Week 12, change from baseline		
Mean (SD)	-4.6 (5.3)	-4.8 (6.3)
Median (minimum, maximum)	-3.3 (-19.0, 5.8)	-4.8 (-21.0, 8.5)
LS mean (SE) [a]	-4.4 (0.8)	-4.3 (0.9)
95% CI	(-6.0, -2.8)	(-6.1, -2.6)
LSM difference from placebo (SE) [a]	-0.1 (1.1)	
95% CI	(-2.2, 2.1)	
p-value	0.9633	

CI=confidence interval; CSU=chronic spontaneous urticaria; ISS7=weekly Itch Severity Score; LS=least squares; mITT=modified Intent-to-Treat; SD=standard deviation; SE=standard error; UAS7=weekly Urticaria Assessment Score; U.S.=United States.

[a] Based on a mixed model for repeated measures using data censored without imputation including fixed effects for baseline value, omalizumab experience for the treatment of CSU, UAS7 (16–27, 28–42), country (U.S., non-U.S.), treatment, study week, the treatment-by-week interaction, and the baseline by-week interaction and allowing for random subject effects.

Source: Table 14.2.2.3a

Proportion of subjects achieving UAS7=0 at Week 12

Overall in the mITT population, 6.3% of subjects in the lirentelimab group were considered UAS7 responders at Week 12 compared with none of the subjects in the placebo group (Table 5). However, the proportion of UAS7 responders in the lirentelimab group was not significantly different than in the placebo group (risk difference versus placebo of 6.25 [95% CI: -11.40, 23.78], p=0.1201).

A similar pattern was observed in the PP population (risk difference versus placebo of 6.78 [95% CI: -11.44, 24.94], p=0.1190; Table 14.2.2.4b).

Table 5 Proportion of Subjects Achieving UAS7 of 0 at Week 12 (mITT Population)

	Lirentelimab (N=64)	**Placebo (N=59)**
Week 12 UAS7 responders	4 (6.3)	0
Week 12 UAS7 non-responders	60 (93.8)	59 (100)
95% CI [a]	(1.73, 15.24)	(0.00, 6.06)
Risk difference vs placebo	6.25	
95% CI for risk difference [b]	(-11.40, 23.78)	
p-value [c]	0.1201	

CI=confidence interval; mITT=modified Intent-to-Treat; UAS7=weekly Urticaria Assessment Score.
Note: A Week 12 responder is defined as a UAS7 of 0 at Week 12. Subjects with missing Week 12 UAS7 are considered non-responders.
[a] 95% CI for the binomial UAS7 response.
[b] Exact 95% confidence limits.
[c] p-value from Fisher's Exact test comparing lirentelimab versus placebo.
Source: Table 14.2.2.4a.

Eosinophil Levels

Consistent with previously reported antibody-dependent cellular cytotoxicity (ADCC) activity of lirentelimab on eosinophils, subjects treated with lirentelimab showed sustained depletion of blood eosinophil counts. In the Safety population, lirentelimab-treated subjects' blood eosinophils decreased by 80.5% versus placebo-treated subjects' blood eosinophils, which increased minimally by 5.4% on Day 1 post injection during the double-blind period. Decrease in eosinophils in lirentelimab group persisted throughout the duration of the double-blind period of the study (Table 14.3.2.1).

Overall, depletion of peripheral blood eosinophil was sustained during the OLE period. From AK002-027 baseline in the Safety population, absolute peripheral blood counts of eosinophils decreased by 75.5% overall on OLE Day 1 post injection (66.9% for subjects in the placebo rollover group and 83.7% for subjects in the lirentelimab continuing group) and by 84.3% overall on OLE Day 85 (85.3% for subjects in the placebo rollover group and 83.2% for subjects in the lirentelimab continuing group; OLE Table 14.2.2). From OLE baseline in the Safety population, absolute blood eosinophils counts decreased by 73.7% on OLE Day 1 post injection and by 92.5% on OLE Day 85 for subjects in the placebo rollover group. For subjects in the lirentelimab continuing group the absolute eosinophil counts remained low throughout OLE Day 85 (OLE Table 14.2.2).

In the 6 subjects, whose absolute eosinophil count was monitored in the extended safety follow-up, the lower absolute eosinophil counts were not considered clinically significant by the investigator. Out of the 6 subjects enrolled in the safety follow-up period 3 subjects completed the study at OLE Day 211 and the remaining 3 subjects were referred for additional evaluation and follow-up with their treating physician.

Safety

Extent of Exposure and Compliance

The majority of subjects (117 [92.1%] subjects overall, 61 [92.4%] subjects in the lirentelimab group and 56 [91.8%] subjects in the placebo group) received 6 doses of study drug during the double-blind period of the study (Table 14.1.7.1). Mean and median duration of exposure were 68.4 and 71.0 days, respectively (range: 1 to 85 days). Overall mean treatment compliance was 95.9% (range: 16.7% to 100.0%; Table 14.1.7.3).

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

In the OLE period, 52 (44.4%) subjects overall (28 subjects in the placebo rollover group and 24 subjects in the lirentelimab continuing group) received 6 doses of study drug (OLE Table 14.1.4.1). Overall, the mean and median duration of exposure were 50.5 and 57.0 days, respectively (range: 1.0 to 79.0 days), and the mean treatment compliance was 74.1% (range: 16.7% to 100.0%; OLE Table 14.1.4.2).

Adverse events

Double-blind period

In the Safety population, all 127 subjects received at least 1 dose of the study drug and majority (117 [92.1%] subjects) completed the study (Table 14.1.1c).

A total of 67 (52.8%) subjects, 36 (54.5%) subjects in the lirentelimab group and 31 (50.8%) subjects in the placebo group, experienced at least 1 TEAE (Table 6). Serious TEAEs were infrequent overall and occurred in 1 subject each in the lirentelimab and placebo groups. TEAEs considered by the investigator as related to study drug were more frequently reported in the placebo group than in the lirentelimab group. TEAESIs were more frequently reported in the lirentelimab group than in the placebo group. TEAEs that led to study drug discontinuation occurred in 2 subjects in the lirentelimab group only. There were no deaths during the study.

Table 6 Overview of Treatment-Emergent Adverse Events (Safety Population)

Number of Subjects With At Least 1 TEAE Category, %	Lirentelimab (N=66)	Placebo (N=61)	Total (N=127)
TEAE [a]	36 (54.5)	31 (50.8)	67 (52.8)
Treatment-related TEAE	26 (39.4)	28 (45.9)	54 (42.5)
Serious TEAE	1 (1.5)	1 (1.6)	2 (1.6)
Treatment-related serious TEAE	1 (1.5)	0	1 (0.8)
TEAE leading to study drug discontinuation	2 (3.0)	0	2 (1.6)
TEAESI	12 (18.2)	5 (8.2)	17 (13.4)
TEAE leading to death	0	0	0

AE=adverse event; TEAE=treatment-emergent adverse event; SC=subcutaneous; TEAESI=TEAE of special interest

[a] TEAEs are AEs occurring with a date of onset (or worsening) on or after the start date of the first SC injection of the study medication.

Source: Table 14.3.1.1

The most common TEAEs (i.e., TEAEs reported in ≥5% of subjects by PT in any treatment group during the study) are shown in Table 7. The most frequently reported TEAEs (≥10% of subjects in any treatment group) were injection site reaction (14 [21.2%] subjects in the lirentelimab group and 6 [9.8%] subjects in the placebo group) and injection related reaction (12 [18.2%] subjects in the lirentelimab group and 5 [8.2%] subjects in the placebo group). The number of events of injection site reaction and injection related reaction was higher in the lirentelimab group (31 and 19 events, respectively) compared with the placebo group (14 and 9 events, respectively).

The incidence of the TEAE of nasopharyngitis was higher in the lirentelimab group (6 [9.1%] subjects) than in the placebo group (3 [4.9%] subjects), whereas the incidence of the TEAE of upper respiratory tract infection was higher in the placebo group (5 [8.2%] subjects) than in the lirentelimab group (2 [3.0%] subjects).

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

Table 7 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=66)		Placebo (N=61)	
	Subjects, n (%)	Events	Subjects, n (%)	Events
At least 1 TEAE	36 (54.5)	126	31 (50.8)	89
General disorders and administration site conditions				
Injection site reaction	14 (21.2)	31	6 (9.8)	14
Injury, poisoning and procedural complications				
Injection related reaction	12 (18.2)	19	5 (8.2)	9
Infections and infestations				
Nasopharyngitis	6 (9.1)	6	3 (4.9)	4
Upper respiratory tract infection	2 (3.0)	2	5 (8.2)	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.

Serious TEAEs occurred in 1 subject each in the lirentelimab and placebo groups (Table 14.3.1.7). The serious TEAEs were epiglottitis obstructive in the lirentelimab group and coronavirus disease 2019 (COVID-19) in the placebo group; the serious TEAE of epiglottitis obstructive was considered possibly related to study treatment (Listing 16.2.3.1.2). The serious TEAE of epiglottitis obstructive was considered treatment related by the Principal Investigator but not by the Medical Monitor; thus, it did not meet expedited reporting requirements in the USA.

Brief summary of serious TEAE is provided below:

- Subject in the lirentelimab group was hospitalized on Day 46 for a serious TEAE of obstructive epiglottitis, which was considered by the investigator as life-threatening and possibly related to study drug. The treatment of obstructive epiglottitis included ceftriaxon, amoxicillin-clavulanate 400-57 mg/mL, dexamethasone, acetaminophen, fentanyl, glycopyrrolate, lidocaine, racepinefrinem, guaifenesin, diphenhydramine, gabapentin, levetiracetam, lorazepam, and iohexol. Subject was discharged on Day 52 and the event was considered resolved. Due to this serious TEAE, the subject discontinued the study drug and then discontinued the study on Day 129.
- Subject in the placebo group was hospitalized on Day 90 for a serious TEAE of COVID-19 infection, which was considered by the investigator as severe and not related to study drug. Subject was discharged on Day 93 and the event was considered resolved. On Day 98 the subject decided to withdraw from the study (Listing 16.2.1.1).

Overall, majority of the TEAEs were of mild or moderate severity (Table 14.3.1.4). A total of 4 (3.1%) subjects experienced severe TEAEs, with higher incidence in the placebo group (3 [4.9%] subjects) than in the lirentelimab group (1 [1.5%] subject). Severe TEAEs included chronic spontaneous urticaria in 1 subject in the lirentelimab group and COVID-19, arthralgia,

and deep vein thrombosis in 1 subject each in the placebo group. In addition, 1 subject in the lirentelimab group had a life-threatening TEAE of epiglottitis obstructive.

TEAEs considered by the investigator as related to study drug were more frequently reported in the lirentelimab group (19 [28.8%] subjects) than in the placebo group (13 [21.3%] subjects; Table 14.3.1.5). The most frequently reported treatment-related TEAEs (at least 5 subjects overall) were injection site reaction (8 subjects in the lirentelimab group and 4 subjects in the placebo group), and injection related reaction (12 subjects in the lirentelimab group and 5 subjects in the placebo group). Another treatment-related TEAEs reported in at least 2 subjects overall was nasopharyngitis (1 subject each in the lirentelimab and placebo groups). All other treatment-related TEAEs were reported in 1 subject each in any treatment group.

Two subjects in the lirentelimab group experienced TEAEs that led to study drug discontinuation, including epiglottitis obstructive and liver function test increased in 1 subject each (Table 14.3.1.6). The TEAE of epiglottitis obstructive was serious, life-threatening, considered by the investigator as possibly related to study drug, and resolved; and the TEAE of liver function test increased was not serious, mild in severity, considered by the investigator as not related to study drug, and recovering at the end of the study (Listing 16.2.3.1.4).

A total of 17 (13.4%) subjects experienced a total of 28 TEAESIs (Table 14.3.1.8). All 28 events were injection related reaction (12 subjects with 19 events in the lirentelimab group and 5 subjects with 9 events 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 57 (48.7%) subjects, 26 (45.6%) subjects in the placebo rollover group and 31 (51.7%) subjects in the lirentelimab continuing group, experienced at least 1 TEAE (OLE Table 14.3.1.1). The overall incidence of TEAEs, treatment-related TEAEs, and TEAESIs in the OLE period was slightly lower than that observed in the double-blind period. No deaths were reported in the OLE period.

The most frequently reported TEAE was injection site reaction (13 [11.1%] subjects overall, 9 subjects in the placebo rollover group and 4 subjects in the lirentelimab continuing group). Other common TEAEs were chronic spontaneous urticaria (8 [6.8%] subjects overall, 2 subjects in the placebo rollover group and 6 subjects in the lirentelimab continuing group), urticaria (8 [6.8%] subjects overall, 5 subjects in the placebo rollover group and 3 subjects in the lirentelimab continuing group), injection related reaction (6 [5.1%] subjects overall, 5 subjects in the placebo rollover group and 1 subject in the lirentelimab continuing group), and nasopharyngitis (6 [5.1%] subjects overall, 1 subject in the placebo rollover group and 5 subjects in the lirentelimab continuing group), and urinary tract infection (6 [5.1%] subjects overall, 1 subject in the placebo rollover group and 5 subjects in the lirentelimab continuing group; OLE Table 14.3.1.2). The number of events of injection site reaction and injection related reaction was higher in the placebo rollover group (22 and 9 events, respectively) compared with the lirentelimab continuing group (7 and 3 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 (4 [3.4%] subjects overall; OLE Table 14.3.1.8). Serious TEAEs were reported in 2 subjects in the placebo rollover (gunshot wound in 1 subject and vertigo and hemiparesis in

1 subject) and 2 subjects in the lirentelimab continuing group (road traffic accident in 1 subject and bipolar disorder and suicidal ideation in 1 subject). None of the serious TEAEs were considered related to study drug, and resolved with or without sequelae (OLE Listing 16.2.3.1.2). The serious TEAEs of bipolar disorder, suicidal ideation, and road traffic accident also led to the discontinuation of study drug and withdrawal from the study.

Brief summary of serious TEAE is provided below:

- Subject in the placebo rollover group was hospitalized on Day 39 for a serious TEAE of gunshot wounds, which was considered life-threatening by the investigator and not related to study drug. Subject was discharged on Day 42 and recovered fully.
- Subject in the placebo rollover group was hospitalized on Day 57 for a serious TEAE of vertigo and hemiparesis, both of which were considered as severe by the investigator and not related to study drug. Subject was discharged on Day 42 and recovered fully.
- Subject in the lirentelimab continuing group was hospitalized on Day 33 for a serious TEAE of bipolar disorder and suicidal ideation, both of which were considered life-threatening by the investigator and not related to study drug. Subject was discharged on Day 43 and the event was considered resolved. Due to this serious TEAE, the subject discontinued the study drug and then discontinued the study on Day 140.
- Subject in the lirentelimab continuing group was hospitalized on Day 8 for a serious TEAE of road traffic accident, which was considered as severe by the investigator and not related to study drug. Subject was discharged on Day 9 and the event was considered resolved. Due to this serious TEAE, the subject withdrew from the study on Day 17.

The majority of TEAEs were mild (16 [13.7%] subjects) or moderate (35 [29.9%] subjects) in severity (OLE Table 14.3.1.4). Severe TEAEs occurred in 4 (3.4%) subjects overall (1 subject in the placebo rollover group and 3 subjects in the lirentelimab continuing group), which included vertigo and hemiparesis in the subject in placebo rollover group and road traffic accident, blood creatine phosphokinase increased, and chronic spontaneous urticaria in the subject in lirentelimab continuing group. In addition, life-threatening TEAEs occurred in 2 (1.7%) subjects overall and included gunshot wound in 1 subject in the placebo rollover group and bipolar disorder and suicidal ideation in 1 subject in the lirentelimab continuing group.

TEAEs considered by the investigator as related to study drug were more frequent in subjects in the placebo rollover group (12 [21.1%] subjects) than in the lirentelimab continuing group (6 [10.0%] subjects). In the placebo rollover group, 7 subjects experienced injection site reaction and 4 subject experienced injection related reaction that were considered by the investigator as related to study drug. In the lirentelimab continuing group, 2 subjects experienced injection site reaction and 1 subject experienced injection related reaction that were considered by the investigator as related to study drug (OLE Table 14.3.1.5). Other treatment-related TEAE reported in 2 subjects overall was diarrhea (2 subjects in the placebo rollover group). All other treatment-related TEAEs were reported in 1 subject in any treatment group.

Five (4.3%) subjects experienced TEAEs that led to study drug discontinuation (OLE Table 14.3.1.6). The events included chronic spontaneous urticaria in 1 subject each in the placebo rollover and lirentelimab continuing groups, bipolar disorder and suicidal ideation in 1 subject in the lirentelimab continuing group, urticaria in 1 subject in the lirentelimab

continuing group, and road traffic accident in 1 subject in the lirentelimab continuing group (OLE Listing 16.2.3.1.4). All subjects with TEAEs that led to study drug discontinuation have recovered except for 1 subject each in the placebo rollover and lirentelimab continuing groups who had a TEAE of chronic spontaneous urticaria. All TEAEs that led to study drug discontinuation also led to study discontinuation (OLE Table 14.3.1.7).

A total of 6 (5.1%) subjects experienced a total of 10 TEAESIs (OLE Table 14.3.1.9). All 10 events were injection related reaction (5 subjects with 7 events in the placebo rollover group and 1 subject with 3 events in the lirentelimab continuing group) and had 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 (Table 14.3.2.1 and Table 14.3.2.2, respectively). 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

There were no clinically meaningful changes in mean values over time in any of the treatment groups in vital signs (Table 14.3.3). Post-baseline abnormal physical examination findings were considered by the investigator as clinically significant in 16 subjects overall (12 subjects in the lirentelimab group and 4 subjects in the placebo group; Listing 16.2.3.8).

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 AK002-027, 127 subjects enrolled in the Safety population and were tested for the presence of serum ADAs. As seen in Table 8, 23 (18.1%) subjects, 5 (7.6%) subjects in the lirentelimab group and 18 (29.5%) subjects in the placebo group, were confirmed positive for ADA at any timepoint during the double-blind period. In the lirentelimab group, 3 (4.5%) subjects were only positive at the predose timepoint. A total of 2 (3.0%) subjects were positive at both predose and postdose timepoints. No subjects were categorized as having treatment-boosted (i.e., postdose titer was at least 4-fold the predose titer) or treatment-induced ADAs (i.e., only postdose positive). No subject in the lirentelimab group exhibited a positive ADA titer at the last visit of the double-blind period.

Table 8 AK002-027 Double-Blind Period ADAs (Safety Population)

ADA Category	Lirentelimab n/N (%)	Placebo n/N (%)
Prevalence: Positive at any visit (pre- and post-dose)[1]	5/66 (7.6%)	18/61 (29.5%)
Only pre-dose positive	3/66 (4.5%)	0/61 (0%)
Both pre- and post-dose positive	2/66 (3.0%)	9/61 (14.8%)
Only post-dose positive (treatment-induced)	0/66 (0%)	9/61 (14.8%)
Boosted pre-existing titers (treatment-boosted) (titer ≥4-fold)	0/66 (0%)	2/61 (3.3%)
Incidence: treatment-induced or treatment-boosted	0/66 (0%)	11/61 (18%)

[1] Predose is defined as Day 1 Baseline in the double-blind period
Source: Listing 16.2.3.9

In the placebo group, no subject was only positive predose, 9 (14.8%) subjects were positive at both pre-and postdose timepoints, and 2 (3.3%) subjects exhibited treatment-boosted ADA titers. A total of 9 (14.8%) subjects were considered to have treatment-induced ADAs. Only 1 subject in the placebo group was positive for ADAs at the last visit in the double-blind period; however, the last visit titer was ≤1 for this subject.

In summary, the overall ADA incidence was higher in the placebo (18.0%) than in the lirentelimab group (0%) during the double-blind period. No subject in either the lirentelimab or placebo group that was positive for ADAs exhibited a titer ≥64 at the last visit in the double-blind period. Therefore, no subject that experienced a SAE or a TEAESI during Study AK002-027 had a positive titer ≥64 at the last visit during the double-blind period.

OLE Period

A total of 118 subjects entered the OLE portion of the study, and 117 subjects received study drug and were in the Safety population. For the enrolled subjects, 115 (98.3%) subjects, 58 subjects in the lirentelimab group and 57 subjects in the placebo rollover group, were tested for ADAs. As seen in Table 9, a total of 28 subjects (24.3%), 9 (15.5%) subjects in the

lirentelimab and 19 (33.3%) subjects in the placebo rollover group, tested positive for ADAs at any timepoint during the OLE period.

In the lirentelimab group, no subjects were positive only predose or both pre- and postdose positive for ADAs. No subject exhibited treatment-boosted ADAs. There were 9 (15.5%) subjects that were only positive for ADAs postdose and categorized as treatment-induced. No subject in the lirentelimab group was positive for ADAs at the last visit in the double-blind period.

Table 9 AK002-027 OLE Period ADAs (Safety Population)

ADA Category	Lirentelimab continuing n/N (%)	Placebo rollover n/N (%)
Prevalence: Positive at any visit (pre- and post-dose)[1]	9/58 (15.5%)	19/57 (33.3%)
Only pre-dose positive	0/58 (0%)	7/57 (12.3%)
Both pre- and post-dose positive	0/58 (0%)	3/57 (5.3%)
Only post-dose positive (treatment-induced)	9/58 (15.5%)	9/57 (15.8%)
Boosted pre-existing titers (treatment-boosted) (titer ≥ 4-fold)	0/58 (0%)	2/57 (3.5%)
Incidence: treatment-induced or treatment-boosted	9/58 (15.5%)	11/57 (19.3%)

1 Predose is defined as before the 1st 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 placebo rollover group, 7 (12.3%) subjects were only positive predose in the OLE period. Three (5.3%) subjects were positive both pre-and postdose and 2 (3.5%) subjects were categorized as having treatment-boosted ADA titers. The ADA incidence was slightly higher in in the placebo group (19.3%) than in the lirentelimab group (15.5%).

In total, 21 subjects were positive for ADAs at the last OLE period visit, 13 with a last visit titer ≤32 and 8 subjects with a last visit titer ≥64. None of the 8 subjects with a positive ADA titer ≥64 experienced a TEAESI (OLE Listing 16.2.3.1.5) during the OLE period. Only 1 subject with an ADA titer ≥64 (OLE Listing 16.2.3.9) experienced SAEs (OLE Listing 16.2.3.1.2) of left-sided weakness and vertigo while on lirentelimab treatment during the OLE period. Neither SAE was considered to be related by the Investigator and the subject recovered.

In summary, there was no indication of an effect of ADA-positive status on safety in Study AK002-027; 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 superior to placebo in improving the UAS7 at Week 12.

Overall, in the mITT population, treatment with lirentelimab reduced the LS mean UAS7 score by 7.9 at Week 12 of the double-blind period of the study to a similar extent as the reduction

with placebo treatment of 8.4. The mean reduction from baseline to Week 12 in the UAS7 score was not significantly different than that in the placebo group. Results from the secondary efficacy endpoints of absolute change from baseline in HSS7 and ISS7 at Week 12 and in the proportion of subjects achieving UAS7 of 0 at Week 12 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 for up to 12 doses and up to 300 mg administered every 2 weeks during the double-blind and OLE periods of the study. In the double-blind portion of the study, a total of 67 (52.8%) subjects, 36 (54.5%) subjects in the lirentelimab group and 31 (50.8%) subjects in the placebo group, experienced at least 1 TEAE. Two (1.6%) subjects experienced serious TEAEs (epiglottitis obstructive in the lirentelimab group and COVID-19 in the placebo group); the serious TEAE of epiglottitis obstructive was considered possibly treatment related. Two (1.6%) subjects (both in the lirentelimab group) experienced TEAEs that led to study drug discontinuation (epiglottitis obstructive and liver function test increased). No deaths were reported during the study.

The most frequently reported TEAEs (≥10% of subjects in any treatment group) were injection site reaction (21.2% in the lirentelimab group and 9.8% in the placebo group) and injection related reaction (18.2% in the lirentelimab group and 8.2% in the placebo group). The number of events of both TEAEs was higher in the lirentelimab group compared with the placebo group. The most frequently reported treatment-related TEAEs (at least 5 subjects overall) were injection site reaction (8 subjects in the lirentelimab group and 4 subjects in the placebo group), and injection related reaction (12 subjects in the lirentelimab group and 5 subjects in the placebo group).

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 H1-AH refractory CSU achieving improvements from baseline in UAS7 score at Week 12 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 TEAE was injection site reaction. Lirentelimab appeared to be well tolerated in long-term dosing.

Date of the Report: 23 July 2024

References

Shankar 2014

Shankar G, Arkin S, Cocea L, Devanarayan V, Kirshner S et al. American Association of Pharmaceutical Scientists. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. AAPS J. 2014 Jul;16(4):658-73.