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

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Clinical Research Protocol AK002-027

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Approval: [redacted]

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[redacted], MD, [redacted] Date

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Investigator Protocol Agreement

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

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Protocol Amendment 4: **22 September 2023**

Investigator Printed Name: _____

Investigator Signature: _____

Date: _____

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List of Abbreviations

[redacted]	[redacted]
AC	Allergic conjunctivitis
ACS	Allergic Conjunctivitis Symptom(s)
ADA	Anti-drug-antibody
ADCC	Antibody-dependent cellular cytotoxicity
ADL	Activities of daily living
AE	Adverse event(s)
AESI	Adverse event(s) of special interest
AKC	Atopic keratoconjunctivitis
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Anti-HBc	Antibody to Hepatitis B core antigen
Anti-HCV	Hepatitis C virus antibody
AST	Aspartate aminotransferase
CBC	Complete blood count
CFR	Code of Federal Regulation
CHOLUAS7	Cholinergic urticaria assessment score
CI	Confidence interval
cm	Centimeter
CMH	Cochran-Mantel-Haenszel (test)
COVID-19	Coronavirus disease 2019
CS	Clinically significant
CSU	Chronic spontaneous urticaria
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trials Facilitation and Coordination Group
CU	Chronic urticaria
[redacted]	[redacted]
EAACI	European Academy of Allergy and Clinical Immunology
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDF	European Dermatology Forum

EG	Eosinophilic gastritis
ELISA	Enzyme-linked immunosorbent assay
EoD	Eosinophilic duodenitis (formerly referred to as eosinophilic gastroenteritis)
EoE	Eosinophilic esophagitis
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
FUP	Follow-up
GA^{2}LEN	Global Allergy and Asthma European Network
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation (European Union)
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
H1-AH	H1-antihistamine
H2-AH	H2-antihistamine
HBsAg	Hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
hCG	human chorionic gonadotropin
HSS	Hives Severity Score
ICE	Intercurrent event(s)
ICF	Informed consent form
ICH	International Council on Harmonisation
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IND	Investigational New Drug (application)
IP	Investigational product
IRB	Institutional Review Board

IRR	Infusion-related reaction (intravenous infusion) Injection-related reaction (subcutaneous injection)
IRT	Interactive Response Technology (system)
ISM	Indolent systemic mastocytosis
ISR	Injection site reaction
ISS	Itch Severity Scale
ITIM	Immunoreceptor tyrosine-based inhibitory motif
ITT	Intent to treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVIG	Intravenous immunoglobulin
JAK	Janus kinase(s)
kg	Kilogram
LARC	Long-Acting Reversible Contraceptives
LLN	Lower limit of normal
LS	Least square (mean)
LTRA	Leukotriene receptor antagonist(s)
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intention-to-Treat
mIU	Milli-international units
mL	Milliliter
mM	Millimolar
mTOR	mammalian Target of Rapamycin
NCI	National Cancer Institute
NCS	Not clinically significant
NOAEL	No-observed-adverse-effect level
NOEL	No-observed effect level
PD	Pharmacodynamics
PEF	Peak expiratory flow
PID	Patient identification number

PK	Pharmacokinetic(s)
PP	Per Protocol
PRO	Patient reported outcome
[redacted]	[redacted]
SAE	Serious adverse event(s)
SAP	Statistical Analysis Plan
SC	Subcutaneous
SE	Standard error
Siglec	Sialic acid-binding, immunoglobulin-like lectin
SOC	System organ class
TEAE	Treatment-emergent adverse event(s)
TEAESI	Treatment-emergent adverse event(s) of special interest
TNF	Tumor necrosis factor
µL	Microliter
UAS7	Urticaria Assessment Score
[redacted]	[redacted]
ULN	Upper limit of normal
UPDD	Urticaria Patient Daily Diary
USP	United States Pharmacopeia
VKC	Vernal conjunctivitis
w/v	Weight/Volume
WAO	World Allergy Organization
WOCBP	Women of childbearing potential

1. Protocol Synopsis

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., 825 Industrial Road, Suite 500, San Carlos, CA 94070.
Number of Sites:	Up to 70 clinical centers in the United States, Germany, and Poland
Number of Subjects:	Approximately 130

Nonclinical Background

Lirentelimab (AK002) is a humanized non-fucosylated immunoglobulin G1 (IgG1) monoclonal antibody directed against Siglec-8, a member of the CD33-related family of sialic acid-binding, immunoglobulin-like lectins (Siglecs). Siglec-8 has a restricted tissue distribution, expressed selectively on the surface of mature eosinophils and mast cells, but not in early precursors of these cell populations. In blood, binding of lirentelimab to Siglec-8 induces antibody-dependent cellular cytotoxicity (ADCC) against eosinophils, leading to rapid and sustained depletion of these cells from the circulation. In tissue, lirentelimab induces direct apoptosis of eosinophils and inhibition of mast cells.

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

Clinical Background

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

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

Study AK002-017 evaluated the pharmacokinetics (PK) and pharmacokinetics (PD) of lirentelimab IV and SC in healthy volunteers. Subjects received 0.3, 1, 3, or 5 mg/kg or a fixed dose of 300 mg or 450 mg lirentelimab SC, or 1 mg/kg or 3 mg/kg lirentelimab IV. In each of the SC cohorts, 8 subjects were randomized to lirentelimab (6 per group) or placebo (2 per group) in a double-blind manner; 12 subjects received lirentelimab IV (6 subjects per group) in an open-label manner.

Clinical Background cont.

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

Lirentelimab IV was previously studied in an open-label study in subjects with CU refractory to treatment with non-sedating H1-antihistamines (H1-AH). The design was intended to assess the efficacy and safety of lirentelimab in both omalizumab-naïve chronic spontaneous urticaria (CSU) and chronic inducible urticaria (cholinergic and dermatographic subtypes), as well as subjects with CSU refractory to omalizumab treatment.

Efficacy was assessed by subject reported outcome assessments using the urticaria control test (UCT), urticaria assessment score (UAS7), cholinergic urticaria assessment score (CHOLUAS7), as well as various quality of life measures. The primary efficacy endpoint was change in UCT from baseline at Week 22. At baseline, all subjects had uncontrolled CU, defined as a UCT <12. At Week 22, UCT increased in all subject cohorts. Within each disease cohort, statistically significant improvements from baseline were observed in disease symptoms with many subjects reporting well controlled disease (UCT >12).

UAS7 was assessed in subjects with CSU. At Week 22, the mean % reductions in UAS7 from baseline mean change was -73.2% for the omalizumab-naïve CSU (CSU-XN) group (mean = -13.9, 95% CI = -19.5 to -8.4), and -46.6% for the omalizumab-failure CSU (CSU-XF) group (mean = -14.0, 95% CI = -21.0 to -7.0).

Supplementary analysis of UAS7 evaluated clinical response (UAS7 ≤6) and complete response (UAS7 = 0 or ≥90% reduction from baseline). Clinical response was met by over 60% of subjects in the CSU-XN disease cohort and 55% in the omalizumab failure group.

In addition, complete responses were observed in 53.8% of subjects in CSU-XN and 9.1% in CSU-XF group. Lirentelimab IV was well tolerated with IRR being the most common adverse event (AE). As mentioned above, the SC formulation has been well tolerated with no IRR to date.

These efficacy and safety data suggest that lirentelimab may have a role in the treatment of subjects with various subtypes of antihistamine-resistant urticaria including subjects who have failed omalizumab.

Target Disease Background and Rationale

Chronic spontaneous urticaria (CSU) is a skin condition, which is characterized by transient and unpredictable pruritic wheal and flare type skin reactions, and, in some subjects, the occurrence of angioedema. There are >500,000 people estimated to have CU in the US, most of whom are women or adults ≥40 years of age (Wertenteil, 2019). In Europe, more than 5 million subjects are thought to suffer from persisting urticarial symptoms (Maurer, 2011), which either occurs spontaneously (i.e., spontaneous urticaria), or can be induced as a result of environmental physical stimuli such as pressure, ultraviolet irradiation, heat or cold (physical urticaria), or by other means (Metz, 2012).

Target Disease Background and Rationale cont.

Subjects with CU are often severely impaired in their quality of life (Mlynek, 2009), with negative effects on sleep, daily activities, school/work life, and social interactions, and psychiatric comorbidity being frequent. The duration of the disease is generally several years but is likely to be longer in more severe cases, cases with concurrent angioedema, in combination with physical urticaria, or with a positive autologous serum skin test (autoreactivity). It also has a large impact on society in terms of direct and indirect health care costs, as well as reduced performance at work and in private life (Maurer, 2011). In many subjects, an underlying cause of CSU cannot be identified, making a causal and/or curative treatment difficult.

The European EAACI/GA2LEN/EDF/WAO Guideline states that the aim of treatment for all types of urticaria is to achieve complete symptom relief (Zuberbier, 2014). However, most subjects with CSU and all subjects with inducible urticaria require symptomatic treatment for effective symptom control. The current treatment guidelines for the management of all forms of urticaria recommend the use of non-sedating oral H1-AH as first-line therapy. In more than 50% of subjects, symptoms persist despite dosing of antihistamines up to 4 times the licensed dose (Maurer, 2011). In antihistamine-refractory subjects with CSU, the only currently licensed treatment is omalizumab, a monoclonal anti-IgE antibody. In subjects with inducible urticaria, including CU, no other licensed drugs are available and subjects often need to be treated with omalizumab, cyclosporin, or other off-label drugs (Metz, 2014a; Metz, 2014b).

In double-blind placebo-controlled studies in selected H1-AH refractory subjects, omalizumab has been shown to be effective in the treatment of CSU and is recommended as third-line therapy if symptoms persist with 4-fold antihistamines. However, a substantial number of CSU subjects continue to have symptoms despite omalizumab treatment or do not respond at all to omalizumab treatment. Therefore, there is a significant unmet need for new targeted therapeutic options for subjects with CSU.

As described above, lirentelimab was studied in various forms of spontaneous and inducible urticaria in an open-label study. The results of that study provide a strong rationale for conducting a randomized, double-blind study in CSU.

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

- Chronic CSU that has been diagnosed and present for at least 6 months at the time of screening.
- Subjects who are refractory to treatment with H1-AH, either omalizumab-exposed or omalizumab naïve.
- At the screening visit the subject must have presence of hives and itch for at least 6 consecutive weeks.
- At the time of randomization the subject must have a UAS7 score of at least 16 (range 0–42) and a HSS7 score of at least 8 (range 0–21) during the 7 days prior to randomization.

Target Disease Background and Rationale cont.

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

Rationale for Dose Selection

A dosing regimen of 300 mg lirentelimab SC administered every 2 weeks for 6 doses is proposed. This regimen is based on PK modeling for Study AK002-017, comparing dose regimens of the IV infusion doses vs. the SC injection doses administered every 28 days. These simulations showed that a dose of 300 mg lirentelimab SC provided a substantially lower C_{max} and slightly lower 1-month trough level than 3 mg/kg lirentelimab IV. Discussion with experts participating in dermatologic trials with biologics and reports of external data from other compounds targeting other type 2 dermatological conditions such as atopic dermatitis support the use of higher or more frequent dosing in cutaneous diseases than in other allergic conditions (i.e., asthma). Dose-response relationships and results across multiple endpoints show trends toward improved efficacy with increasing dose and duration and suggest that further increases in dose or treatment duration might improve efficacy. In CSU, clinical response to omalizumab has been demonstrated to be dose dependent across multiple clinical trials (Metz, 2020; Zhao, 2015).

Furthermore, reports of omalizumab updosing beyond licensed doses in the real-world treatment setting of CSU demonstrate success in clinical response that exceeds those reported in clinical trials, with a safety profile similar to that reported in clinical trials. The use of doses higher than the licensed dose of omalizumab 300 mg provides support to recommend the use of higher doses of other immuno-modulating therapies, especially for subjects who are partial responders or non-responders and refractory to treatment. Consequently, increasing the frequency of the 300 mg lirentelimab SC dose from every 4 weeks to every 2 weeks is proposed for the AK002-027 study.

Simulations using AK002-017 study data indicate that a fixed dose of lirentelimab SC 300 mg every 2 weeks is expected to provide greater exposure than 300 mg administered monthly without an increased C_{max}, in contrast to the 3 mg/kg IV dose. The proposed SC dose and frequency of administration is expected to provide higher steady state levels as supported by the safety and tolerability profile of lirentelimab IV in subjects with other eosinophilic and mast cell diseases. The concentration of 150 mg/mL lirentelimab SC is consistent with an injection volume of 2 mL for the 300 mg dose, which was well tolerated without injection site reactions in Study AK002-017. When proof of concept is established, other lirentelimab SC doses and schedules may be explored.

Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of lirentelimab in omalizumab-naïve or exposed adult subjects with H1-AH refractory CSU. Subjects enrolled in the study will receive 6 doses of lirentelimab SC or placebo SC administered every 2 weeks followed by the option to enroll in the open-label extension (OLE) period, contingent on defined selection criteria, to receive 6 doses of 300 mg lirentelimab SC every 2 weeks. Subjects will be observed for a post-treatment period of 12 weeks.

Study Design cont.

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

Subjects will be consented and then screened for up to 3 weeks. Subjects who have been on a stable, approved dose regimen of 2nd generation or later H1-AH prior to screening will undergo a 2-week eligibility screening period. Subjects who are not on a stable approved dose regimen of 2nd generation or later H1-AH will be allowed an additional 1 week during the screening period during which they must reach a stable approved dosing regimen before entering the 2-week eligibility screening period.

Stable approved doses of H1-AH for study purposes is defined as a H1-AH regimen between 1x and 4x 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 be established by Day -14 (14 days prior to randomization) for purposes of the screening eligibility period. Baseline disease activity data will be collected with daily assessment of itch and hive severity, both of which will be used to calculate a weekly urticaria activity score (UAS7). Subjects who meet eligibility criteria at both Day -7 and Day 1 can be enrolled into the study. The baseline UAS7 score for efficacy analysis calculations will be defined by the 7-day period prior to randomization.

Eligible subjects will receive 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 will continue to receive subsequent doses on Days 15, 29, 43, 57, and 71, for a total of 6 doses. Subjects will remain 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 IRR, the subject may require prolonged observation (>1 hour or until the symptoms resolve), as per Investigator's discretion. Subjects will also be instructed to immediately contact the study team if any reactions occur after discharge.

During the treatment period, subjects will return to the site for study visits as described in the Schedule of Events. Subjects will have the option to enter an open-label extension (OLE) period of the study to receive 6 doses of 300 mg lirentelimab SC contingent on meeting defined study selection criteria. All subjects will be followed for another 12 weeks after the last dose in the randomized double-blind period or OLE period.

The primary endpoint will be assessed at Week 12, i.e., 2 weeks after the last dose in the double-blind period of the study. Subjects will be stratified at randomization based on omalizumab experience for the treatment of CSU (exposed/naïve) and UAS7 score (16–27 or 28–42).

Study Design cont.

At selected US sites, fresh biopsies of lesional (if available) and nonlesional skin may be collected from subjects predose and post-dose. Providing biopsies is optional.

Primary Objective and Endpoint

The primary objective of the study will be to characterize the efficacy of lirentelimab SC in adult subjects with CSU as assessed by the absolute change in UAS7 from baseline to Week 12.

Secondary Objectives and Endpoints

To further characterize the efficacy and safety of lirentelimab in adult subjects with CSU as measured by the following:

1) Improvement of severity of hives assessed as absolute change from baseline in Hives Severity Score (HSS7) at Week 12.
2) Improvement of severity of itch assessed as absolute change from baseline in Itch Severity Scale (ISS7) at Week 12.
3) Absence of hives and itch at Week 12 assessed as proportion of subjects achieving UAS7 = 0.
4) Occurrence of treatment-emergent adverse events (TEAE) and serious adverse events (SAE), laboratory values, vital signs, and physical examinations during the study.

Exploratory Objectives and Endpoints

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

1) Impact on subject's [redacted] based on change in [redacted] at Week 12 compared with baseline.
2) Impact on subject's [redacted] at Week 12 and Week 22 assessed as proportion of subjects achieving [redacted].
3) Impact on [redacted] at Week 12 and Week 22 assessed as proportion of subjects achieving [redacted].
4) Impact on [redacted] at Week 12 and Week 22 assessed as proportion of subjects achieving [redacted]

Safety Objectives

To evaluate the safety and tolerability of lirentelimab SC in adult subjects with H1-AH refractory CSU by determining AE incidence and severity, study withdrawals due to AE, changes in vital signs and laboratory tests including immunogenicity and changes in concomitant medication beginning on or after the first injection of study drug.

Study Population

Approximately 130 subjects with H1-AH refractory CSU are expected to be randomized in this study. Subjects will be randomized 1:1 in a double-blind manner to receive:

- 6 doses of 300 mg lirentelimab SC every 2 weeks
- 6 doses of placebo SC every 2 weeks

Subject Selection Criteria

Inclusion Criteria: Subjects with CSU are eligible for the study if they meet all of the following criteria.

1) Subject is able to understand the information on the study, has the capacity to consent, and has provided written informed consent.
2) Male and 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 score (range 0–42) ≥16 and HSS7 score (range 0–21) ≥8 during the 7 consecutive days prior to the screening Day -7 Phone Visit and during the 7 consecutive days prior to randomization (Day 1).
5) Subjects that 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 be on stable dose of H1-AH, between 1x and 4x of the licensed dose and at the licensed frequency, for treatment of CSU for at least 1 week prior to screening and 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.
8) Female subjects must be either postmenopausal (defined as no menses for 12 months without an alternative medical cause) with FSH level >30 mIU/mL at screening or surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months, or if of childbearing potential, have a negative serum pregnancy test and agree to use a highly effective method of contraception as defined in this protocol or abstain from sexual activity, if compliant with preferred and usual lifestyle of the subject from screening until the end of the study or for 120 days following the last dose of study drug, whichever is longer.

   In the case of a postmenopausal female subject with FSH level ≤30 mIU/mL at screening, the subject will be required to have a negative serum pregnancy test during the screening period and

will also be required to have a negative urine dipstick pregnancy test prior to dosing and at each study visit.

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

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

1) 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 a 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) Use of any of the following treatments within 4 weeks prior to the baseline visit or any condition that in the opinion of the Investigator is likely to require such treatment(s) during the first 4 weeks of study treatment.
   - 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., benralizumab, pramipexole)
   - Routine (daily or every other day during 5 or more consecutive days) doses of systemic hydroxychloroquine
   - Plasmapheresis

5) Use of oral Janus kinase (JAK) inhibitors within 8 weeks of the baseline visit (requires discussion with Medical Monitor prior to subject enrolling in study).

6) Use of any of the following treatments within 3 weeks prior to the baseline visit:
   - H2 Antihistamines (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 (LTRA) (e.g., montelukast, zafirlukast)

7) H1-AH use at greater than approved doses or greater than local CSU guideline recommended doses after Screening Visit 1.

Subject Selection Criteria – Exclusion Criteria cont.

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 is longer.
   - Other biologics, including investigational biologics (e.g., dupilumab, omalizumab, benralizumab, etc.) and TNF inhibitors (e.g., infliximab, adalimumab), within 5 half-lives if known or 8 weeks prior to the baseline visit, whichever is longer.
   - Intravenous immunoglobulin (IVIG) within 5 half-lives
9) Planned or anticipated use of any prohibited medication.
10) Subjects having 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 that informed consent is obtained and has not been treated with or has 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 are 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 is longer, for biologic products).

Subject Selection Criteria – Exclusion Criteria cont.

23) Subjects who weigh <40 kg at screening.

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

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

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

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

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

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

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

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

Test Product, Dose, and Administration

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

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

Test Product, Dose, and Administration cont.

Dosing (lirentelimab SC or placebo SC) will comprise a single 2 mL SC injection administered in the front of the thigh with a 27-gauge SC needle. Six doses of lirentelimab SC or placebo SC will be administered biweekly over 10 weeks.

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

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

Following the double-blind period of the study, subjects will have the option to enter the OLE period of the study, contingent on meeting certain study criteria. Subjects will receive 6 doses of 300 mg lirentelimab SC during the OLE period.

Duration of Subject Participation

The total study duration for each subject in the double-blind period of the study will be approximately 6 months. If a subject chooses to enter the OLE period, the total study duration will be approximately 9 months, which includes the following:

- Screening period of approximately 2–3 weeks prior to study drug administration.
- Treatment period of 10 weeks (administration of lirentelimab SC or placebo SC every 2 weeks for 6 doses).
- Optional OLE period of 10 weeks (administration of lirentelimab SC every 2 weeks for 6 doses).
- Follow-up period of 12 weeks after the last dose of study drug in the OLE period. Subjects who do not enter the OLE period of the study will be followed for 12 weeks after the last dose in the double-blind period of the study.

Efficacy Evaluations

Primary Efficacy Endpoint: The primary efficacy endpoint in the study will be the absolute change in UAS7 at Week 12 compared with baseline.

Secondary Efficacy Endpoints:

1) Improvement of severity of hives assessed as absolute change from baseline in HSS7 at Week 12.
2) Improvement of severity of itch assessed as absolute change from baseline in ISS7 at Week 12.
3) Complete absence of hives and itch at Weeks 12 assessed as proportion of subjects achieving UAS7 = 0.
4) Occurrence of TEAE and SAE, laboratory values, vital signs, and physical examinations during the study.

Exploratory Efficacy Endpoints:

1) Impact on subject's [redacted] based on change in [redacted] at Week 12 vs baseline.

Exploratory Efficacy Endpoints cont.

2) Impact on subject's [redacted] at Week 12 and Week 22 assessed as proportion of subjects achieving [redacted].
3) Impact on [redacted] at Week 12 and Week 22 assessed as proportion of subjects achieving [redacted]
4) Impact on [redacted] at Week 12 and Week 22 assessed as proportion of subjects achieving [redacted]

Safety Evaluation

Safety and tolerability will be assessed throughout the study by monitoring and evaluating AE, including reactions to the SC injection. All TEAE will be collected from the start of study drug administration through Day 155 (±5 days) or Early Termination (ET).

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

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

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

Pharmacokinetic and Anti-Drug-Antibody Evaluation

Pharmacokinetic (PK) blood samples will be collected for assessment of lirentelimab concentrations using a validated enzyme-linked immunosorbent assay (ELISA) method. Pharmacokinetic blood samples will be obtained predose on Days 1, 15, 29, 43, 57, 71, 85, 127, and 155 (or ET) and in between Dose 1 and Dose 2 on Day 8. Additional PK samples will be collected in the OLE period of the study. Blood (serum) will be collected for assessment of lirentelimab anti-drug antibodies (ADA) using a validated assay method. ADA blood samples will be obtained predose on Days 1, 29, 43, 85, and 155 (or ET) and in between Dose 1 and Dose 2 on Day 8 and in the event of a suspected immunogenicity-related AE. Additional ADA samples will be collected in the OLE period of the study.

Sample Size Calculation

A sample size of approximately 55 evaluable subjects per treatment group will provide >90% power to demonstrate a statistically significant difference between lirentelimab SC and placebo SC in absolute change in UAS7. We hypothesized a mean difference of at least 8 between lirentelimab SC and placebo SC and a pooled standard deviation of 11. This calculation is based on results derived from the AK002-006 study and expected placebo response rates reported in previously published data in H1-AH refractory CSU.

Additionally, randomization of up to approximately 130 subjects (65 per treatment group) will further support the evaluation of safety and tolerability of lirentelimab SC.

Statistical Analysis

All subjects who receive study medication will be included in the Safety population for safety analysis. Subjects who are randomized and have received at least 1 dose of study medication will be included in the modified Intent-to-Treat (mITT) population for efficacy analysis. mITT subjects who have received all 6 injections of study drug and do not have major protocol deviations possibly interfering with the interpretation of efficacy and safety assessment will be included in the Per Protocol (PP) population.

When appropriate, summary statistics of number of non-missing values, mean, median, standard deviation, minimum, and maximum will be computed for continuous variables and summary statistics of number and proportion will be computed for categorical variables.

Two-sided 95% confidence intervals (CI) will be provided for the mean and proportion. No formal statistical inferences will be made for safety parameters. Safety data will be summarized for each treatment group.

Baseline for safety analysis is defined as the last observation before administration of the first dose of study drug. Baseline for efficacy endpoints derived from daily diary assessments will be based on the 7 days before administration of the first dose of study drug.

Subjects will be stratified at randomization based on omalizumab experience for the treatment of CSU (exposed/naïve) and UAS7 score (16–27 or 28–42).

The primary endpoint will be analyzed by analysis of covariance (ANCOVA). The least square (LS) mean, standard error (SE), and 95% CI for each treatment group, and the between group difference will be derived from ANCOVA with treatment as a factor, baseline UAS7 (continuous), and omalizumab experience for the treatment of CSU (exposed or naïve) as covariates. Data on subjects who experience an intercurrent event (ICE, i.e., exit the study prematurely or initiate prohibited or rescue medications) prior to the end of Week 12 will be set to missing. Missing UAS7 will be imputed using the Markov Chain Monte Carlo (MCMC) method. Detailed specifications for the missing data imputation will be provided in the Statistical Analysis Plan (SAP).

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

Change from baseline in continuous secondary outcomes measured at multiple post-baseline time points will be analyzed longitudinally using a mixed model. The model will include fixed effects for baseline value, randomization stratification factor, treatment, week, treatment by week interaction, baseline value by week interaction, and allow for random subject effects. The model variance-covariance matrix will be unstructured. However, if computation does not converge, the variance-covariance matrix will take the form of Toeplitz, AR (1), and compound symmetry, whichever converges first. The Kenward-Rogers approach for computing denominator degrees of freedom will be used to account appropriately for pooling of within-subject and between-subject variance estimates. Least square means and the 95% CI for the between-group difference will be estimated for each week.

Statistical Analysis cont.

Subject incidence of TEAE will be tabulated by MedDRA System Organ Class and Preferred Term and by severity and treatment relationship. Serious TEAE and TEAE leading to study discontinuation will be listed with pertinent information. Change from baseline in laboratory tests will be summarized with descriptive statistics. Details will be provided in the SAP.

2. Background

2.1 Siglec-8 and Lirentelimab

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

2.2 Overview of Nonclinical Studies

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

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

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

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

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

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

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

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

2.3 Overview of Clinical Studies

Lirentelimab IV, administered as a monthly intravenous infusion, has previously been tested in over 700 healthy volunteers and in subjects with indolent systemic mastocytosis (ISM), chronic urticaria (CU), severe allergic conjunctivitis (AC), mast cell gastritis, eosinophilic gastritis (EG) and/or eosinophilic duodenitis (EoD), and eosinophilic esophagitis (EoE). Multiple monthly doses of 3 mg/kg have been given to subjects with ISM, CU, severe AC, EG and/or EoD, and EoE.

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

Study AK002-017 evaluated the PK and PD of lirentelimab IV and SC in healthy volunteers. Subjects received 0.3, 1, 3, or 5 mg/kg or a fixed dose of 300 mg or 450 mg lirentelimab SC, or 1 mg/kg or 3 mg/kg lirentelimab IV. In each of the SC cohorts, 8 subjects were randomized to lirentelimab (6 per group) or placebo (2 per group) in a double-blind manner; 12 subjects received lirentelimab IV (6 subjects per group) in an open-label manner.

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

Lirentelimab IV was previously studied in an open-label study in subjects with CU, who were omalizumab-naïve and refractory to treatment with non-sedating H1-antihistamines (H1-AH), and in some subjects with chronic spontaneous urticaria (CSU) refractory to omalizumab. The

design was intended to assess the efficacy and safety of lirentelimab in both CSU and chronic inducible urticaria (cholinergic and dermatographic subtypes) refractory to standard treatment.

Efficacy was assessed by subject reported outcome assessment, using the urticaria control test (UCT), urticaria assessment score (UAS7), cholinergic urticaria assessment score (CHOLUAS7), as well as various quality of life measures. The primary efficacy endpoint was change in UCT from baseline at Week 22. At baseline, all subjects had uncontrolled CU as determined using UCT <12. At Week 22, UCT increased in all subject cohorts. Within each disease cohort, the 95% confidence intervals (CI) for the mean changes signified significant improvement in moving subjects from an initial state of poorly controlled disease to well-controlled disease.

UAS7 was assessed in CSU subjects only. At Week 22, the mean reductions in UAS7 from baseline (% change) were statistically significant:

- CSU (omalizumab-naïve, XN) group: mean = -13.9, 95% CI = -19.5 to -8.4 (% change = -73.2, 95% CI = -94.9 to -51.4)
- CSU (omalizumab-failure, XF) group: mean = -14.0, 95% CI = -21.0 to -7.0 (% change = -46.6, 95% CI = -71.0 to -22.2)

Supplementary analysis of UAS7 evaluated complete response (UAS7 = 0 or ≥90% reduction from baseline) and clinical response (UAS7 ≤6). Clinical response was met by over 60% of subjects in the CSU-XN disease cohort and 55% in the omalizumab failure group. In addition, complete responses were observed in 53.8% of subjects in CSU-XN and 9.1% in CSU-XF group. Lirentelimab IV was well tolerated, with IRR being the only significant adverse event (AE) related to the intravenous formulation.

Taken together, these efficacy and safety data suggest that lirentelimab may have a role in the treatment of various subtypes of antihistamine-resistant urticaria, including subjects who have failed omalizumab.

2.4 Chronic Urticaria

Chronic spontaneous urticaria (CSU) is a skin condition, which is characterized by transient and unpredictable pruritic wheal and flare type skin reactions and, in some subjects, the occurrence of angioedema. There are >500,000 people estimated to have CU in the US, most of whom are women or adults ≥40 years of age (Wertenteil, 2019). In Europe, more than 5 million subjects are thought to suffer from persisting urticarial symptoms (Maurer, 2011), which either occurs spontaneously (i.e., spontaneous urticaria), or can be induced as a result of environmental

physical stimuli such as pressure, ultraviolet irradiation, heat or cold (physical urticaria), or by other means (Metz, 2012).

Subjects with CU are often severely impaired in their quality of life (Mlynek, 2009), with negative effects on sleep, daily activities, school/work life, and social interactions, and psychiatric comorbidity being frequent. The duration of the disease is generally several years but is likely to be longer in cases that are more severe, cases with concurrent angioedema, in combination with physical urticaria, or with a positive autologous serum skin test (autoreactivity). It also has a large impact on society in terms of direct and indirect health care costs, as well as reduced performance at work and in private life (Maurer, 2011). In many subjects, an underlying cause of CSU cannot be identified making a causal and/or curative treatment difficult. Figure 1 provides a classification of chronic urticaria subtypes (Zuberbier, 2014), and Figure 2 presents an example of CU.

The European EAACI/GA^{2}LEN/EDF/WAO Guideline states that the aim of treatment for all types of urticaria is to achieve complete symptom relief (Zuberbier, 2014). However, most subjects with CSU and all subjects with inducible urticaria require symptomatic treatment for effective symptom control.

The current treatment guidelines for the management of all forms of urticaria recommend the use of non-sedating oral H1-AH as first-line therapy. In more than 50% of the subjects, symptoms persist despite dosing of antihistamines up to 4 times the licensed dose (Maurer, 2011). In antihistamine-refractory subjects with CSU, the only currently licensed treatment is omalizumab, a monoclonal anti-IgE antibody. In subjects with inducible urticaria, including CU, no other licensed drugs are available, and subjects often need to be treated with omalizumab, cyclosporin, or other off-label drugs (Metz, 2014a; Metz, 2014b).

In double-blind placebo-controlled studies in selected H1-AH refractory subjects, omalizumab has been shown to be effective in the treatment of CSU and is recommended as third-line therapy if symptoms persist with 4-fold antihistamines. However, a substantial number of CSU subjects continue to have symptoms despite omalizumab treatment or do not respond at all to omalizumab treatment. Therefore, there is a significant unmet need for new targeted therapeutic options for subjects with CSU.

As described above, lirentelimab was studied in various forms of spontaneous and inducible urticaria in an open-label study. The results of that study provide a strong rationale for conducting a randomized, double-blind study in CSU.

Chronic urticaria subtypes	
Chronic spontaneous urticaria	Inducible urticaria
Spontaneous appearance of wheals, angioedema, or both ≥6 weeks due to known or unknown causes	Symptomatic dermographism* Cold urticaria† Delayed pressure urticaria‡ Solar urticaria Heat urticaria§ Vibratory angioedema Cholinergic urticaria Contact urticaria Aquagenic urticaria
* Also called *urticaria factitia*, dermographic urticaria † Also called cold contact urticaria ‡ Also called pressure urticaria § Also called heat contact urticaria	

(Zuberbier, 2014)

Figure 1 Classification of Chronic Urticaria

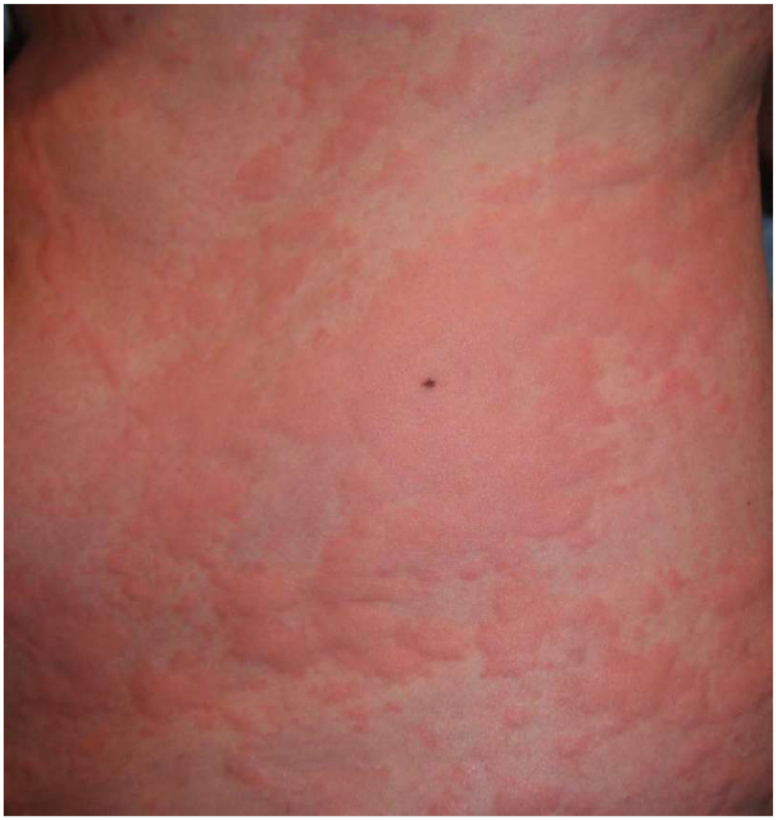


Figure 2 Subject with Chronic Urticaria: Spontaneous Wheal, Flare, and Itch

2.5 Benefit–Risk Assessment

In the treatment of CSU, there remains an unmet medical need for more effective and safe therapies. The goal of therapy, as outlined in current treatment guidelines, is to achieve complete control of the disease, but despite this some patients continue to have symptoms that remain bothersome. Standard first-line treatment of CSU consists of the use of nonsedating H1-antihistamines (H1-AH) at locally approved doses, with escalation up to four times the approved dose used off-label as second-line treatment. For those patients that have uncontrolled disease despite optimized H1-AH therapy, current guidelines recommend omalizumab as third-line therapy to be used in addition to H1-AH (Zuberbier, 2014). However, the treatment of H1-AH refractory patients cannot be fully met by omalizumab as more than half of subjects with CSU in registrational studies continued to experience symptoms despite omalizumab treatment (Maurer, 2013). In addition, other biologics tested in controlled clinical trials have failed to demonstrate benefit in omalizumab refractory subjects leaving a population in particular need of a safe and effective therapy (Sanofi, 2022).

Results from nonclinical studies demonstrate that lirentelimab has the potential to provide clinical benefit to patients with diseases in which eosinophils and mast cells play a pathogenic role, particularly CSU. In vitro, in vivo, and human ex vivo studies have shown that lirentelimab binds specifically to Siglec-8-positive cells (eosinophils, mast cells, and to a lesser degree basophils), reduces the number of blood and tissue eosinophils, inhibits the activation of mast cells, and decreases the release of eosinophil-derived and mast cell-derived inflammatory mediators, offering an attractive and unique therapeutic approach for difficult-to-treat diseases such as CSU, atopic dermatitis, and others. In clinical studies of lirentelimab conducted in more than 700 subjects (healthy volunteers and patients with eosinophilic diseases), the maximum tolerated dose (MTD) for lirentelimab in humans has not been reached. Lirentelimab is generally well tolerated, with mild to moderate IRR as the most common AE. A total of five related cases of IRR SAEs have been reported to date, all of which resolved within 24 hours without sequelae or fatalities. Of note, all IRR AEs and SAEs occurred when lirentelimab was administered intravenously and most often occurred in association with the first infusion.

Preliminary evidence of clinical activity in CU (including CSU) has been obtained in a phase 2 open-label study with lirentelimab IV in subjects who were omalizumab-naïve and refractory to treatment with non-sedating H1-AH, as well as some subjects with chronic spontaneous urticaria (CSU) refractory to omalizumab (Altrichter, 2022). In this study, a total of 45 patients were enrolled in 4 cohorts (n=13 omalizumab-naive CSU, n=11 omalizumab-refractory CSU, n=11 CholU, n=10 symptomatic dermographism). Urticaria Control Test scores were noted to increase with lirentelimab across the cohorts, with mean changes at week 22 of 11.1 ± 4.1, 4.8 ± 7.0, 6.5 ±

6.2, and 3.4 ± 4.1 and complete response rates (Urticaria Control Test score ≥ 12) of 92%, 36%, 82%, and 40%, respectively. In omalizumab-naive and omalizumab-refractory patients with CSU, disease activity decreased at week 22 (mean UAS7 change, -73% and -47%, respectively), with UAS7 response rates (≥ 50% reduction) of 77% and 45%, respectively. Most commonly reported adverse events included infusion-related reactions (43%; all mild/moderate and transient), nasopharyngitis (21%), and headache (19%) and no treatment-related serious adverse events were reported during this study. The results of the study supported evidence of efficacy based on significant improvement of subject reported outcome assessments, using the urticaria control test (UCT), and urticaria activity score (UAS7), as well as various quality of life measures across both omalizumab naïve and omalizumab refractory patients.

The Sponsor has developed a lirentelimab formulation that can be administered subcutaneously (lirentelimab SC). A Phase 1 study of lirentelimab SC in 36 healthy volunteers demonstrated that lirentelimab SC was also well tolerated and achieved eosinophil depletion at a level comparable to that of lirentelimab IV. In this study, no lirentelimab SC-treated subjects reported local or systemic injection-related reactions were reported. This subcutaneous formulation is currently being used in a Phase 2 atopic dermatitis clinical trial and will be used for the current CSU study.

The overall benefit-risk assessment of lirentelimab appears to be positive. Clinical safety data observed from over 700 exposed subjects suggest that lirentelimab is generally well tolerated and presents an acceptable safety profile to date. There is a significant unmet need for additional treatment options for patients with CSU refractory to H1-antihistamines, and particularly those whose symptoms are also refractory to omalizumab as no effective therapeutic options currently exist. Results from the Phase 2a lirentelimab study in CU suggest that lirentelimab may be an effective treatment for CSU patients, for both omalizumab naïve and omalizumab refractory subjects. Adequately powered double-blind, placebo-controlled randomized studies are warranted to further characterize lirentelimab as a potential treatment option for H1-AH refractory CSU.

3. Rationale for Study and Dose Selection

3.1 Rationale for Study Design

The approach utilized in this study is consistent with current international EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI guidelines that recommend add-on therapy with a biologic (e.g., anti-IgE biologic therapy) for H1-AH refractory CSU patients after trying therapeutic options such as guideline-recommended H1-AH dose escalation up to 4x the licensed dose (Zuberbier, 2022). Nevertheless, the use of sustained, higher than licensed doses of H1-AH varies in practice between countries and may not be feasible or tolerated in some subjects. For

example, higher than licensed doses of newer H1-AHs were reported to be associated with dystonia and psychoactive effects (Garg, 2018; Tashiro, 2004).

The flexibility provided in the current international guidelines allows for addition of other treatments such as omalizumab prior to maximizing H1-AH dosage to 4x. The omalizumab indication for CSU sets no minimum, required dose titration of H1-AH before starting the therapy (EMA, 2023).

The study design includes the continuous use of stable doses of H1-AH treatment throughout the study. To qualify for study entry, the investigator must ensure that subjects with CSU remain symptomatic while receiving stable doses of H1-AH, i.e., 'refractory' to 1-4x the licensed dose of H1-AH. This would avoid excluding subjects that may benefit from biologic treatment due to H1-AH drug intolerance to above labeled doses. Furthermore, the use of stable doses of H1-AH ranging at 1-4x the licensed dose as background therapy for CSU clinical trials is consistent with industry standard for studies evaluating novel pharmacological therapies for the treatment of H1-AH refractory CSU subjects.

3.2 Rationale for Dose Selection

A dosing regimen of 300 mg lirentelimab SC administered every 2 weeks for 6 doses is proposed. This regimen is based on pharmacokinetic (PK) modeling for Study AK002-017, comparing dose regimens for the IV infusion doses vs. the SC injection doses administered every 28 days. These simulations showed that a dose of 300 mg lirentelimab SC provided a substantially lower C_{max} and slightly lower 1-month trough level than 3 mg/kg lirentelimab IV.

Discussion with experts participating in dermatologic trials with biologics and reports of external data from other compounds targeting other type 2 dermatological conditions such as atopic dermatitis support the use of higher or more frequent dosing in cutaneous diseases than in other allergic conditions (i.e., asthma). Dose-response relationships and results across multiple endpoints show trends toward improved efficacy with increasing dose and duration and suggest that further increases in dose or treatment duration might improve efficacy. In CSU, clinical response to omalizumab has been demonstrated to be dose-dependent across multiple clinical trials (Metz, 2020; Zhao, 2015).

Furthermore, reports of omalizumab up-dosing beyond licensed doses in the real-world treatment setting of CSU demonstrate success in clinical response that exceeds those reported in clinical trials, with a safety profile similar to that reported in clinical trials. The use of doses higher than the licensed dose of omalizumab 300 mg provides support to recommend the use of higher doses of other immunomodulating therapies, especially for subjects who are partial responders or non-

responders and refractory to treatment. Consequently, increasing the frequency of the 300 mg lirentelimab SC dose from every 4 weeks to every 2 weeks is proposed for the AK002-027 study.

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

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

4. Study Objectives

4.1 Primary Objective and Endpoint

The primary objective of the study will be to characterize the efficacy of lirentelimab SC in omalizumab-naïve and omalizumab-exposed adult subjects with H1-AH refractory CSU as assessed by the absolute change from baseline in UAS7 at Week 12.

4.2 Secondary Objectives and Endpoints

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

1) Improvement of severity of hives assessed as absolute change from baseline in Hives Severity Score (HSS7) at Weeks 12.
2) Improvement of severity of itch assessed as absolute change from baseline in Itch Severity Scale (ISS7) at Weeks 12.
3) Complete absence of hives and itch at Weeks 12, assessed as proportion of subjects achieving UAS7=0.
4) Occurrence of treatment-emergent adverse events (TEAE) and serious adverse events (SAE), laboratory values, vital signs, and physical examinations during the study.

4.3 Exploratory Objectives and Endpoints

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

1) Impact on subject's [redacted] based on absolute change in [redacted] at Week 12 compared with baseline.
2) Impact on subject's [redacted] at Week 12 and Week 22 assessed as proportion of subjects achieving [redacted].
3) Impact on [redacted] at Week 12 and Week 22 assessed as proportion of subjects achieving [redacted].
4) Impact on [redacted] at Week 12 and Week 22 assessed as proportion of subjects achieving [redacted]

4.4 Safety Objectives

To evaluate the safety and tolerability of lirentelimab in adult subjects with H1-AH refractory CSU by determining AE incidence and severity, study withdrawals due to AE, 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.

Safety and tolerability will be assessed throughout the study by monitoring and evaluating AE, including any reactions to the SC injection. All TEAE will be collected from the start of study drug administration through Day 155 (±5 days) or Early Termination (ET) during the double-blind period of the study.

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

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

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

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

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

5. Study Design

5.1 Study Overview

This is a Phase 2, proof-of-concept, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of lirentelimab in adult subjects with moderate-to-severe H1-AH refractory CSU. Subjects enrolled in the study will receive 6 doses of 300 mg lirentelimab SC or placebo SC administered every 2 weeks, followed by the option to enroll in the open-label extension (OLE) period, contingent on defined selection criteria, to receive 6 doses of 300 mg lirentelimab SC. Subjects will be observed for a post-treatment period of 12 weeks.

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

Subjects will be consented and then screened for up to 3 weeks. Subjects who have been on a stable, approved dose regimen of 2nd generation or later H1-AH prior to screening will undergo a 2-week eligibility screening period. Subjects who are not on a stable approved 2nd generation or later H1-AH dose regimen will be allowed an additional 1 week during the screening period during which they must reach a stable approved dosing regimen before entering the 2-week eligibility screening period.

Stable approved doses of H1-AH for study purposes is defined as an 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 be established by Day -14 (14 days prior to randomization) for purposes of the screening eligibility period. Baseline disease activity data will be collected with daily assessment of itch and hives severity, both of which will be used to

calculate a weekly UAS7. Subjects who meet eligibility criteria at both Day -7 and Day 1 can be enrolled in the study.

The baseline UAS7 score for efficacy analysis calculations will be defined by the 7-day period prior to randomization. To ensure there is sufficient patient-reported outcome (PRO) data at baseline, a subject should complete at least four daily PRO questionnaires per week for a minimum period of the seven days prior to Day 1.

Subjects who meet eligibility criteria at Day -7 and Day 1 can be enrolled into the study. Subjects will not be allowed to rescreen for inadequate PRO compliance or PRO scores not meeting the minimum requirements (UAS7 ≥16, or HSS7 ≥8).

Aside from the exclusion noted above, subjects may be allowed to be rescreened once after consultation and agreement with the Medical Monitor. Subjects rescreened within 30 days of signing initial consent will not need to reconsent if there are no changes to the ICF.

Eligible subjects who meet selection criteria at screening and baseline will receive 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 will continue to receive subsequent doses on Days 15, 29, 43, 57, and 71 for a total of 6 doses. Subjects will remain 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 injection-related reaction (IRR), the subject may require prolonged observation (>1 hour or until the symptoms resolve), as per Investigator's discretion. Subjects will also be instructed to immediately contact the study team if any reactions occur after discharge.

During the treatment period, subjects will return to the site for study visits as described in the Schedule of Events. Subjects will have the option to enter an OLE period of the study to receive 6 doses of lirentelimab contingent on meeting defined study selection criteria. Subjects will be followed for another 12 weeks after the last dose. Subjects not entering the OLE period will be followed for 12 weeks after the last dose of study drug in the double-blind period.

The primary endpoint will be assessed at Week 12, i.e., 2 weeks after the last dose in the double-blind period of the study. Subjects will be stratified at randomization based on omalizumab experience for the treatment of CSU (exposed/naïve) and UAS7 score (16–27 or 28–42).

At selected US sites, fresh biopsies of lesional (if available) and nonlesional skin may be collected from subjects predose and post-dose. Providing biopsies is optional.

5.2 Schedule of Events and Study Diagram

The overall schedule of assessments and procedures is described in Table 1. The study diagram is presented in Figure 3.

Table 1 Study AK002-027 Schedule of Assessments: Double-Blind Period

Assessment/Procedure Description	Screening			Double-Blind Treatment Period (10 weeks)							Double-Blind Follow-Up Period (12 weeks)		
	Day -21[25]	~Day -14[26]	Day -7 (±3) Baseline	Day 1 (±3) Baseline / Dose 1	Day 8 (±3)	Day 15 (±5) / Dose 2	Day 29 (±5) / Dose 3	Day 43 (±5) / Dose 4	Day 57 (±5) / Dose 5	Day 71 (±5) / Dose 6	Day 85 (±5)	Day 127 (±5)	Day 155 (±5)
	Week -3	Week -2	Week -1 Phone Visit	Week 0	Week 1 Visit	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12 FUP-1	Week 18 FUP-2	Week 22 FUP-3/EOS
	<-------Diary Eligibility Phase[24]--			---------->									
Informed consent	X	X[26]											
Demographics	X	X[26]											
Medical History	X	X[26]	X	X									
Detailed previous diagnosis and treatments review[1]	X	X[26]											
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Confirm H1-AH usage	X	X	X	X	X	X	X	X	X				
Body weight and height[2]	X	X[26]		X	X	X	X	X	X	X	X	X	X
Vital signs[3]	X	X[26]		X	X	X	X	X	X	X	X	X	X
10-lead or 12-lead ECG[4]	X	X[26]											
Complete physical exam[5]	X	X[26]											
Symptom-directed physical exam[6]				X	X	X	X	X	X	X	X	X	X
UPDD[7]	<----------Complete daily from Screening through Day 155 or 84 days post last dose---------->												
UAS7[8]		X	X	X	X	X	X	X	X	X	X	X	X
[redacted][9]	X	X		X			X		X		X	X	X
[redacted][10]	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood for serology	X	X											
Atopic Conditions Questionnaire[11]				X							X		

Assessment/Procedure Description	Screening			Double-Blind Treatment Period (10 weeks)							Double-Blind Follow-Up Period (12 weeks)		
	Day -21[25]	~Day -14[26]	Day -7 (±3) Baseline	Day 1 (±3) Baseline / Dose 1	Day 8 (±3)	Day 15 (±5) / Dose 2	Day 29 (±5) / Dose 3	Day 43 (±5) / Dose 4	Day 57 (±5) / Dose 5	Day 71 (±5) / Dose 6	Day 85 (±5)	Day 127 (±5)	Day 155 (±5)
	Week -3	Week -2	Week -1 Phone Visit	Week 0	Week 1 Visit	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12 FUP-1	Week 18 FUP-2	Week 22 FUP-3/EOS
	<-------Diary Eligibility Phase[24]--			---------->									
Blood for total serum IgE[12]	X	X						X		X	X	X	X
Blood for chemistry (includes hCG; FSH for screening period only)[13]	X	X		X		X	X	X	X	X	X	X	X
Blood for CBC with differential[14]	X	X		X		X	X	X	X	X	X	X	X
Blood for PK[15]				X	X	X	X	X	X	X	X	X	X
Blood for ADA[16]				X	X		X	X			X		X
Urine for dipstick pregnancy test[17]				X	X	X	X	X	X	X	X	X	X
Urine for urinalysis[18]	X	X									X		X
Eligibility assessment	X	X	X	X									
Access IRT: Stratification and randomization[19]				X									
Access IRT: IP kit assignment				X		X	X	X	X	X			
Study drug administration				X		X	X	X	X	X			
Non-serious adverse events[20]				X	X	X	X	X	X	X	X	X	X
Serious adverse events[21]		X	X	X	X	X	X	X	X	X	X	X	X
Biopsy collection (optional)[22]				X[22]					X[22]				
Begin OLE period after Day 85 assessments, if applicable[23]												Day 127 and Day 155 visits do not apply to OLE subjects[23]	

ADA: Anti-lirentelimab antibody
CBC: Complete Blood Count
[redacted]
EOS: End of Study
FSH: Follicle-Stimulating Hormone
FUP: Follow-up
hCG: Human Chorionic Gonadotropin
IP: Investigational Product
IRT: Interactive Response Technology
UAS7: Weekly Urticaria Activity Score
[redacted]
UPDD: Urticaria Patient Daily Diary

Table 1 Notes

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

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

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

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

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

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

7) All subjects will be provided with the UPDD. Subjects will receive clear instructions on the completion of the diary. UPDD includes UAS7 (itch and hives) for CSU subjects for clinical symptoms, and activity interference. Activate daily PRO and have subject complete first PRO (UPDD) in the clinic at Screening. To ensure there is sufficient PRO data at baseline, subject should complete at least four daily PRO questionnaires during the seven days prior to Day 1.

8) The UAS7 is the sum for 7 days of the daily Hives Severity Score (HSS) and the daily Itch Severity Scale (ISS) based on information collected in the UPDD and will be assessed weekly.

9) The [redacted] is a [redacted] questionnaire for assessing [redacted] and will be administered to the subject when in clinic.

10) The [redacted] be completed by those subjects that also have a history of [redacted]

11) Subjects will be prompted to answer additional questions about symptoms related to asthma, allergic rhinitis, and allergic conjunctivitis.

12) Blood samples for total serum IgE will be collected during screening, predose on Days 43 and 71, on follow-up Days 85, 127, and 155 or 14, 56, and 84 (±5) days after the last dose of study drug if early termination (ET).

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

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

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

16) Blood for ADA will be collected predose on dosing Days 1, 29, and 43, as well as on Day 8 (±3), and on follow-up Days 85 and 155 (14 and 84 [±5] days after last dose of study drug if ET). The ADA sample will also be collected any time an immunogenicity-related AE occurs.

17) Urine will be collected for dipstick pregnancy test on all dosing days, Day 8, and all follow-up days (14, 56, and 84 [±5] days after last dose of study drug if ET) for all subjects of childbearing potential. Test kits will be supplied by the central laboratory. Tests will be completed on site and evaluated prior to each SC injection.

18) Urine for standard urinalysis will be obtained at screening and on follow-up Days 85 and 155 (14 and 84 [±5] days if ET), and symptom-based, as necessary.

19) Randomization will be conducted through the IRT system. Subjects will be randomized 1:1, 300 mg lirentelimab SC or placebo SC. They will be stratified based on biologic status and UAS7 score at baseline.

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

21) The reporting of serious adverse events (SAE) occurring after signing the ICF and prior to the first SC injection will be limited to those that relate to screening procedures. The capture of all SAE and AE that are not related to screening procedures will begin at the time of first SC injection of study drug.

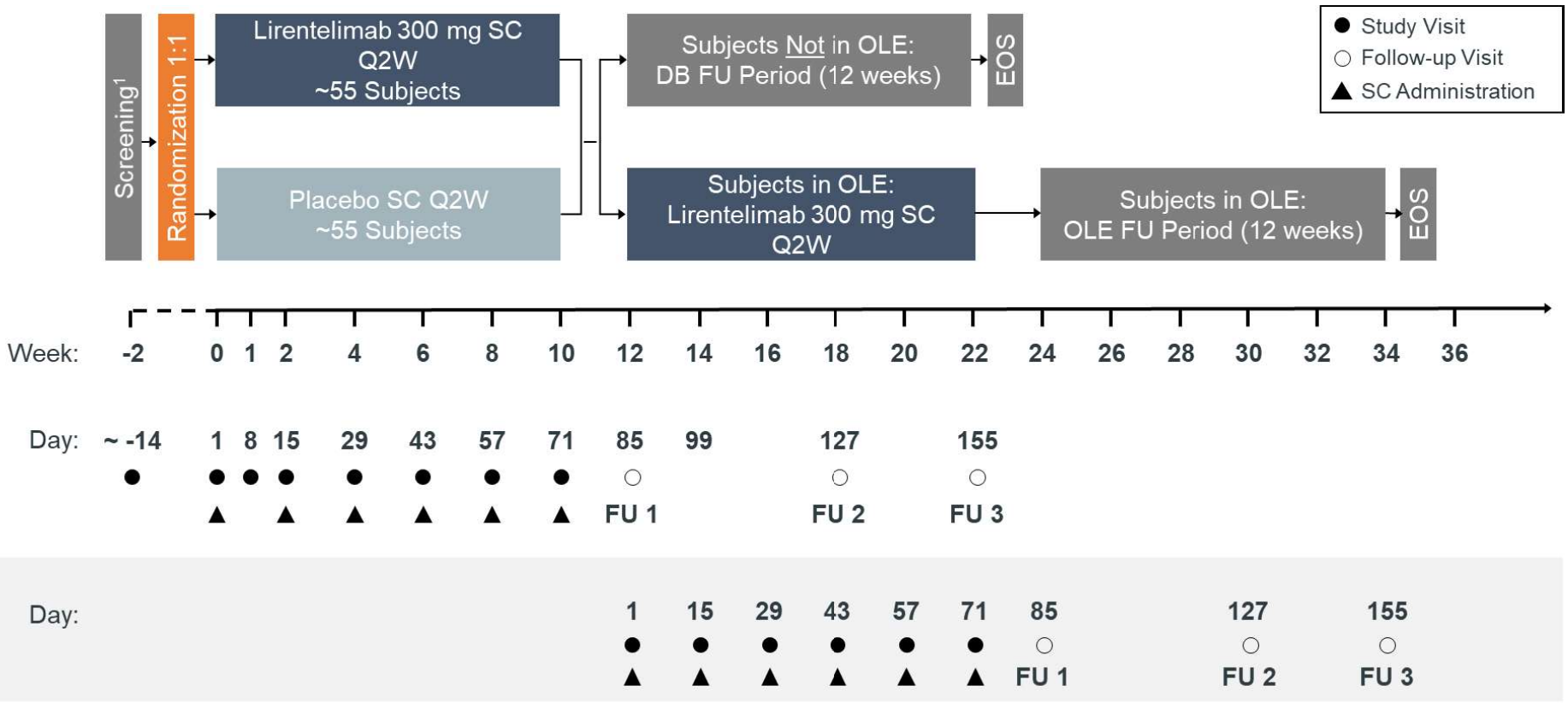
22) Lesional (if available) and nonlesional skin biopsies will be collected at selected US sites and is optional for subjects. Biopsies may be collected at baseline/predose on Day 1 and post-dose on either Day 57, Day 71, or Day 85. See Section 12.1.11.

23) Open-label extension dosing may start on Day 85 after all Day 85 procedures are conducted or within 7 days after the Day 85 visit. Subjects who decide to enter the OLE period and meet the selection criteria for the OLE period will follow the schedule of events in Appendix 9.

24) The diary eligibility period will be 3 weeks for subjects that are screened but not on stable approved doses of H1-AH for at least a week prior to screening. They will enter screening at Day -21 and be stabilized on H1-AH. Subjects will start completing the UPDD the day they start screening. The diary eligibility period will be 2 weeks for subjects that are screened and on stable approved doses of H1-AH for at least a week prior to screening. These subjects will enter screening at Day -14. Subjects will have to meet the UAS7 and HSS7 criteria at Day -7 and again at Day 1, along with other entry criteria in order to qualify for the study.

25) Subjects will either have a 3-week screening period (subjects who are not on a stable dose of H1-AH) or a 2-week screening period (subjects who are on a stable dose of H1-AH) depending on H1-AH usage at the time of screening (refer to Table Note #24).

26) If assessment was performed at Day -21, it is not required to repeat at Day -14.



[1]Subjects entering screening without prior medication history of using a stable, approved dose of H1-AH for at least 7 days prior to Screening Day need to start at ~Day -21 instead

DB=Double-blind period; FU=Follow Up; SC=subcutaneous; OLE=Open Label Extension

Figure 3 Study Diagram

6. Estimand Considerations

The estimand for the AK002-027 study estimates the effect of treatment, while considering treatment adherence and response. The estimand will provide an answer to the question that is crucial to individual subjects: "If I take this study medication as part of my treatment regimen, without adding any further drugs that may impact the underlying disease or exit the study prematurely, what improvement in CSU might be anticipated after 12 weeks?"

Target of Estimation

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

Population Targeted by the Scientific Question

The population targeted by the scientific question is defined by the inclusion and exclusion criteria as part of the study protocol. Subjects may be male or female and must have a clinical diagnosis of CSU as defined by the study inclusion criteria.

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

The primary endpoint to be obtained for each subject in this study to address the scientific question is the UAS7 score at Week 12.

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

The following intercurrent events (ICE) will be anticipated and addressed:

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

For the analysis of the estimand, UAS7 scores will be set to missing from the point when an ICE occurs.

7. Criteria for Evaluation

7.1 Safety Endpoints

The safety and tolerability of lirentelimab SC will be assessed by determining the incidence, relationship to study drug, and severity of TEAE, withdrawals due to AE, and changes in vital

signs, laboratory tests, changes in concomitant medication use due to AE, immunogenicity, and other safety parameters. These endpoints will be based on the following:

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

7.2 Pharmacokinetic Endpoints

Blood (serum) will be collected for assessment of lirentelimab concentrations using a validated enzyme-linked immunosorbent assay (ELISA) method. Pharmacokinetic blood samples will be obtained predose on Days 1, 15, 29, 43, 57, 71, 85, 127, and 155 (or ET) and on Day 8 between Dose 1 and Dose 2. Additional PK samples will be collected in the OLE period of the study.

Blood (serum) will be collected for assessment of lirentelimab anti-drug antibodies (ADA) using a validated assay method. ADA blood samples will be obtained predose on Days 1, 29, and 43, on follow-up days 85 and 155 (or ET), on Day 8 between Dose 1 and Dose 2, and in the event of a suspected immunogenicity-related AE. Additional ADA samples will be collected in the OLE period of the study.

7.2.1 Primary Efficacy Endpoints

The primary endpoint will be the absolute change from baseline in UAS7 at Week 12 (Day 85).

7.2.2 Secondary Efficacy Endpoints

Secondary endpoints will be:

1) Improvement of severity of hives assessed as absolute change from baseline in HSS7 at Week 12.

2) Improvement of severity of itch assessed as absolute change from baseline in ISS7 at Week 12.

3) Complete absence of hives and itch at Weeks 12 assessed as proportion of subjects achieving UAS7 = 0.

4) Occurrence of TEAE and SAE, laboratory values, vital signs, and physical examinations during the study.

7.2.3 Exploratory Efficacy Endpoints

1) Impact on subject's [redacted] based on change in [redacted] at Week 12 vs baseline.

2) Impact on subject's [redacted] at Week 12 and Week 22 assessed as proportion of subjects achieving [redacted].

3) Impact on [redacted] at Week 12 and Week 22 assessed as proportion of subjects achieving [redacted]

4) Impact on [redacted] at Week 12 and Week 22 assessed as proportion of subjects achieving [redacted]

8. Subject Selection

8.1 Number of Subjects

Approximately 130 subjects with H1-AH refractory urticaria are expected to be randomized in this study. Subjects will be randomized 1:1 in double-blind manner to receive:

- 6 doses of 300 mg lirentelimab SC every 2 weeks
- 6 doses of placebo SC every 2 weeks

8.2 Number of Sites

Up to 70 clinical centers in the United States, Germany, and Poland.

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

8.3 Study Population

Approximately 130 male and female subjects with H1-AH refractory urticaria will be enrolled in the study. Subjects will be either biologic-naïve or biologic-exposed. Biologic-exposed subjects include those who have demonstrated secondary loss of response, intolerance, or lack of access to biologics due to economic reasons.

8.4 Inclusion Criteria

Subjects with CSU are eligible to enroll in the study if they meet all of the following criteria.

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

2) Male and 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 score (range 0–42) ≥16 and HSS7 score (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 that 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 be 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 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.

8) Female subjects must be either postmenopausal (defined as no menses for 12 months without an alternative medical cause) with FSH level >30 mIU/mL at screening or surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months or, if of childbearing potential, have a negative serum pregnancy test and agree to use a highly effective method of contraception as defined in this protocol or abstain from sexual activity,

if compliant with preferred and usual lifestyle of the subject, from screening until the end of the study or for 120 days following the last dose of study drug, whichever is longer.

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

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

8.5 Exclusion Criteria

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

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

   – 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) Use of oral Janus kinase (JAK) inhibitors within 8 weeks of the baseline visit (requires discussion with Medical Monitor prior to subject enrolling in study).

6) Use of 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 (LTRA) (e.g., montelukast, zafirlukast)

7) H1-AH use 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 is longer.
   - Other biologics, including investigational biologics (e.g., dupilumab, omalizumab, benralizumab, etc.) and TNF inhibitors (e.g., infliximab, adalimumab) within 5 half-lives if known or 8 weeks prior to baseline visit, whichever is longer.
   - Intravenous immunoglobulin (IVIG) within 5 half-lives

9) Planned or anticipated use of any prohibited medication.

10) Subjects having 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 that informed consent is obtained and has not been treated with or has 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 are 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 is longer, for biologic products).

23) Subjects who weigh <40 kg at screening.

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

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

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

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

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

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

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

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

8.6 Safety Evaluations

Safety and tolerability will be assessed throughout the study by monitoring and evaluating AE, including any reactions to the SC injection. All TEAE will be collected from the start of study drug administration through Day 155 (±5 days) or ET for both the double-blind period and OLE period.

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

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

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

9. Prior and Concurrent Medications

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

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

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

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

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

9.1 Prohibited Medications

The introduction of medications or therapies for other medical conditions known to affect CSU (e.g., systemic corticosteroids, H2-AH, immunosuppressive or immunomodulatory drugs, biologics, hydroxychloroquine, oral doxepin, intravenous IgG, plasmapheresis) are not permitted during the study and during the interval prior to entry into the study as defined in Section 8.5 Exclusion Criteria with the exception of use as rescue therapy.

Topical corticosteroids applied to the skin to manage CSU are prohibited within 7 days prior to baseline visit.

The list of prohibited medications is not considered all inclusive. Medication should be assessed for adherence to the indication and other inclusion/exclusion criteria. The Investigator should instruct the subject to notify the study site about any new medications he/she takes subsequent to receiving the study drug. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered following initial study drug treatment must be listed on the concomitant medications/significant non-drug therapies CRF. Planned or anticipated major medical procedures or surgeries should be avoided during the clinical study.

Any biologics or medications that may interfere with the study efficacy or safety assessments such as systemic immunosuppressive or immunomodulatory drugs or biologics, including but not limited to IL-5 modulators (e.g., benralizumab, reslizumab, mepolizumab), IL-4 and IL-13 antagonists (e.g. dupilumab), 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), TNF inhibitors (e.g., infliximab, adalimumab), anti-IgE antibodies (e.g., omalizumab), eosinophil-depleting drugs (e.g., pramipexole), and systemic corticosteroids are prohibited throughout the study.

Subjects can be omalizumab-naïve or omalizumab-exposed for the treatment of their CSU. Biologic-exposed subjects include those who have demonstrated secondary loss of response, intolerance, or lack of access to biologics due to economic reasons.

Subjects who have demonstrated lack of primary response to treatment with a biologic for their CSU for at least 3 months will not be allowed to participate.

9.2 Allowed Medications

Medications taken for the treatment of CSU, such as 2nd generation or later H1-AH, are allowed during the study, unless prohibited (Section 9.1), and total daily doses are to remain stable during the entire course of the study unless change is required for unforeseen medical necessity. Increases in the dose of H1-AH for CSU symptom management (or other reasons) will be considered rescue therapy, and the subject will be considered a non-responder at the time of the increase in dosage. Subjects should also not decrease the dosage of their H1-AH over the course of the study to prevent confounding of the study results.

Only one H1-AH medication should be used during the study. If more than one H1-AH medications are used prior to screening, subject must reduce to only one stable 2nd generation or later H1-AH and follow the appropriate washout before eligibility screening. All CSU medications used during the screening period and throughout the study will be documented in the CRF. Any allowed medications that are taken must remain stable throughout the study.

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

The vaccine should not be administered within 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.

9.3 Rescue Medications

The use or initiation of any new H1-AH, increase in the total daily dose of an H1-AH, or the use of systemic or topical corticosteroids for the purpose of treating CSU at any point in the study, as compared to baseline, will be considered rescue therapy. Rescue medications are not allowed during the study unless deemed medically necessary at the discretion of the Investigator

(i.e., to treat flare-ups of CSU symptoms) and while subjects will be encouraged to remain in the study following the use of any of these rescue therapies, they will be deemed as treatment non-responders for data evaluation purposes.

Subjects initiating rescue therapy for CSU symptoms or for the treatment of any other medical condition with any of the prohibited medications listed in Section 9.1 that could pose a potential safety risk to the subject (e.g. immunomodulators or other biologic therapies) at any point during the double-blind period of the study will be discontinued from the study but will be followed for the 12-week follow-up period.

The use of systemic corticosteroids at any point during the study for conditions other than CSU is discouraged, and alternative treatments should be considered when possible. If the use of systemic corticosteroids is deemed medically necessary for periods of less than 5 consecutive days to treat conditions other than CSU, the subject may remain in the study at the discretion of the Medical Monitor, and the doses of systemic corticosteroids and reason for administration must be documented as concomitant medications.

10. Study Treatment

10.1 Formulation of Test Product and Placebo

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

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

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

Each dose (lirentelimab SC or placebo SC) will comprise 1 SC injection of 2 mL of study drug administered in the front of the thigh with a 27-gauge SC needle. Maximum volume administered will be 2 mL. Lirentelimab SC or placebo SC (based on randomization assignment)

will be administered on Day 1 (±3), Dose 1; Day 15 (±5), Dose 2; Day 29 (±5), Dose 3; Day 43 (±5), Dose 4; Day 57 (±5), Dose 5; and Day 71 (±5), Dose 6.

Subjects will have the option to enroll in an OLE period to receive 6 doses of 300 mg lirentelimab SC. Subjects will be observed for at least 1 hour after each injection.

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

- The interval between dosing visits must be at least 7 days and no more than 21 days from the previous dosing visit unless directed otherwise by Allakos. The interval count starts the day after the visit and includes the day of the next visit.
- The interval between the final dosing visit and the efficacy visit (Day 85) must be at least 11 days and no more than 17 days from the final dosing visit unless directed otherwise by Allakos. The interval count starts the day after the visit and includes the day of the next visit.

10.2 Study Drug Packaging and Labeling

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

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

10.3 Supply of Study Drug to the Investigational Site

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

10.4 Study Drug Dosage and Dosage Regimen

Subjects will be randomly assigned through the IRT system to an active dose group of 6 doses of lirentelimab SC or placebo SC (Table 2).

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

Table 2 Study Drug Administration

Route	Dose (6 Doses Biweekly Over 10 Weeks)	Total Injection Volume
Subcutaneous	300 mg lirentelimab SC or Placebo SC	2 mL

10.5 Preparation of Study Drug

A study pharmacist or designee will prepare the study drug for the SC injection. On the day of dosing, the designated study pharmacist will prepare lirentelimab or placebo for SC injection. Appropriate aseptic technique will be used, and the drug will be dispensed according to the Pharmacy Manual for AK002-027. Refer to the Pharmacy Manual for additional details.

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

10.6 Study Drug Administration

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

10.7 Study Drug Storage

Study drug will be stored by the study sites at 2°C to 8ºC under lock at the designated pharmacy location. Access will be restricted to designated clinic/pharmacy staff. If the temperature of study

drug storage in the clinic/pharmacy exceeds or falls below this range, the study drug will be quarantined, and the temperature excursion will be reported to the Sponsor or designee. The Sponsor will notify the site if the study drug can to be released from quarantine. Refer to the Pharmacy Manual for additional details.

10.8 Study Drug Accountability

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

11. Subject Numbering, Stratification, Randomization, and Blinding

11.1 Subject Numbering

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

- The first 3 digits designate the study number. For this study, the number is 227.
- The second 3 digits designate the site number.
- The last 3 digits designate the order of consent at the site (the first subject who provides consent is 001, the second subject is 002, etc.).

Subjects will not be allowed to rescreen for inadequate PRO compliance or PRO scores not meeting the minimum requirements (UAS7 $\geq$16, or HSS7 $\geq$8).

Aside from the exclusion noted above, subjects may be allowed to be rescreened once after consultation and agreement with the Medical Monitor. Subjects rescreened within 30 days of signing the initial consent will not need to sign a new ICF providing no changes have been made to the ICF. A new PID will be assigned at the time of rescreening, and the subject will maintain the same PID throughout the study.

11.2 Stratification and Randomization

To be randomized into the study, the subject must have a CSU diagnosis for ≥6 months, refractory to HI-AH. The diagnosis of moderate-to-severe CSU refractory to approved doses of H1-AH at the time of randomization is defined by the presence of hives and itch for ≥6 consecutive weeks prior to Screening Visit 1 and UAS7 score (range 0–42) ≥16 and HSS7 score (range 0–21) ≥8 during the 7 days prior to randomization. The subject must also meet all other applicable inclusion criteria and none of the exclusion criteria.

If the subject qualifies for the study after completing all of the screening procedures, on the day of the first SC injection (Dosing Day 1), the site will access the IRT system in order to stratify and randomize the subject into the study. The IRT system will then randomly assign the subject at an allocation ratio to lirentelimab SC 300 mg or placebo SC for 12 weeks (6 doses) in a double-blind manner and will send an email to the pharmacist and/or designee detailing the kit number(s) to use to prepare the SC injection.

The subject will be stratified based on:

- UAS7 score: 16–27 vs. 28–42.
- Omalizumab experience for the treatment of CSU: omalizumab-exposed vs. omalizumab-naïve.

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

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

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

11.3 Blinding

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

- Access to the randomization codes will be strictly controlled by the IRT system.
- Throughout the double-blind study, the blind should remain unbroken except for an emergency when knowledge of the subject's study medication is necessary for further management or if required for regulatory reporting. The Medical Monitor approves any emergency blind break, if at all possible, prior to the unblinding.
- The lirentelimab SC and placebo SC administered by SC injection will be identical in appearance.
- Results from the analysis of blood samples for PK and ADA will not be provided to the Investigator and Sponsor until after final database lock of the double-blind study.
- Results from the analysis of blood samples for histamine/tryptase tests (collected in case of possible anaphylaxis) will not be provided to the Investigator and Sponsor until after final database lock of the double-blind study, unless required for immediate safety reasons.
- Results of the assessments noted below will not be provided to the Investigator and Sponsor until after final database lock of the double-blind study to avoid bias. The results will be reviewed on an ongoing basis by the Safety Monitor and escalated as appropriate.
  - Differential cell counts including neutrophils, eosinophils, basophils, monocytes, and lymphocytes.

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

11.4 Breaking the Blind

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

If necessary, emergency breaking of the blind can be conducted through the IRT by the Investigator or other registered site users and/or the Medical Monitor. Whenever possible, the Investigator should contact the Medical Monitor before an emergency unblinding. Reason for

unblinding, person conducting the unblinding, personnel who know the unblinded treatment, and date/time of unblinding will be recorded.

12. Study Procedures and Guidelines

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

- At home: The subject should complete the UPDD at home daily. Subjects who have a history of [redacted] should also complete the [redacted].
- At the clinic:
  1) UAS7, [redacted] forms, and Atopic Conditions Questionnaire.
  2) Vital signs will be obtained after the subject has been at rest for ≥5 minutes.
  3) Physical examinations can be performed, and urine samples can be collected either before or after other evaluations, unless otherwise specified.

12.1 Pharmacodynamic/Efficacy-Related Procedures

12.1.1 Urticaria Patient Daily Diary

All subjects will be provided with an Urticaria Patient Daily Diary (UPDD) (Appendix 1). The subjects will receive clear instructions on the completion of the diary. UPDD includes UAS7 (itch and hives) for CSU subjects for clinical symptoms and activity interference. Sub-investigators and subjects will receive appropriate training and guidance on the use of the UPDD.

12.1.2 Weekly Urticaria Activity Score

The UAS7 is the sum for 7 days of the daily Hives Severity Score (HSS) and the daily Itch Severity Scale (ISS) score. The possible range of the weekly UAS7 score is 0–42. Complete UAS7 response is defined as UAS7 = 0 or by reduction of ≥90% from baseline.

12.1.3 Hives Severity Score

The severity of hives will be recorded by all subjects once daily in their UPDD, on a scale of 0 (none) to 3 (>50 hives) (Table 3). A weekly HSS7 is derived by adding the average daily scores of the 7 days preceding the visit. Therefore, the possible range of the weekly score is 0-21. A complete hives response is defined as HSS7 = 0. When one or more of the daily scores are missing, the following principles will be applied to handle the missing data:

- At baseline and post-baseline time points, if a subject has at least 4 non-missing daily scores within a given week, the weekly score is calculated as the sum of the available scores in that week, divided by the number of days that have a non-missing diary score, multiplied by 7.
- At post-baseline time points, if there are less than 4 non-missing daily scores within a given week, then the weekly score is set to missing for the week. Missing data will be imputed using methods outlined in the SAP. It is worth remarking that missing data imputation is not required at baseline since a minimum of 4 daily scores per week are required to determine subject eligibility for the study.

Table 3 Hives Severity Score

Score	Number of Hives per 24 Hours
0	None
1	< 20
2	20-50
3	> 50

12.1.4 Itch Severity Score

The severity of itching will be recorded by all subjects once daily in their UPDD, on a scale of 0 (none) to 3 (severe) (Table 4). A weekly ISS7 is derived by adding the average daily scores of the 7 days preceding the visit. Therefore, the possible range of the weekly score is 0-21. A complete itch response is defined as ISS7 = 0. Partially missing diary entries will be handled in the same way described for the hives severity score.

Table 4 Itch Severity Score

Score	Pruritus (Itch) over the Last 24 Hours
0	None
1	Mild (present but not annoying or troublesome)
2	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Severe (severe itching, which is sufficiently troublesome to interfere with normal daily activity or sleep)

12.1.5 [redacted]

The [redacted] is a [redacted] questionnaire for assessing [redacted] and will be administered to the subject when in the clinic (Appendix 3). Each

item is rated on a scale of [redacted] and a total score is calculated (range, [redacted]). Higher scores indicate [redacted].

12.1.6 [redacted]

The [redacted] is a [redacted] questionnaire used to measure the [redacted] of an affected person (Appendix 4). The format is a simple response [redacted] that assess [redacted] over the past week with an overall scoring system of [redacted] a high score is indicative of a [redacted] is a self-administered questionnaire. Subjects will complete this during screening, Day 8 visit, predose on Days 1, 15, 29, 43, 57, and 71, and during follow-up on Days 85, 127, and 155 or ET.

12.1.7 [redacted]

Subjects that have a history of [redacted] will have to complete the [redacted] daily. The [redacted] is a [redacted], self-administered, daily questionnaire that records [redacted] in subjects with [redacted] (Appendix 2). The format provides [redacted] for each item (scored [redacted]), with a minimum score of [redacted] and a maximum score of [redacted] per day. Lower scores reflect [redacted] and higher scores reflects [redacted]. The [redacted] describes the [redacted] of 7 consecutive days for a score range from [redacted]. Subjects will complete this during screening, Day 8 visit, predose on Days 1, 15, 29, 43, 57, and 71, and during follow-up on Days 85, 127, and 155 or ET.

12.1.8 Atopic Conditions Questionnaire

On Day 1 and Day 85, subjects will be prompted to answer additional questions about severity of symptoms related to asthma, allergic rhinitis, and allergic conjunctivitis (Appendix 5).

12.1.9 Photographs

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

12.1.10 Complete Blood Count with Differential

Blood for CBC with differential, including absolute blood eosinophil count, will be obtained at screening, just prior to each SC injection, and 1 hour (±15 minutes) after the end of each SC injection, as well as on all follow-up days 85, 127, and 155 (±5) or 14, 56, and 84 (±5) days after last dose, if ET. The blood sample will be processed and shipped in accordance with the Laboratory Manual and lab kit instructions. A central laboratory will analyze the blood sample and provide results for CBC with differential including hemoglobin, hematocrit, platelet count,

red blood cell count, white blood cell count, and absolute differential count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils).

During the double-blind period, all differential blood counts from Day 1 (post-dose) through the end of the subject's participation will be blinded to the Sponsor and the site. An unscheduled CBC may be collected at the request of the Safety Monitor. The blood differential test results (neutrophils, eosinophils, basophils, monocytes, and lymphocytes) will be blinded from the Investigator and Sponsor from post-dose Day 1 through Day 155 or ET and until database lock has occurred. If a subject continues to the OLE period of the study, all differential blood counts will be blinded for the first (OLE Day 1) predose assessments and will be unblinded after the subject has received the first dose of the study drug.

As described in the Investigator's Brochure, changes in certain lab results are a part of the expected effects of lirentelimab and could potentially introduce bias in blinded members of the study. The Safety Monitor will have real-time access to these laboratory results and will review and escalate any concerns/issues to the Medical Monitor and/or the site as appropriate. An unscheduled CBC with differential may be collected if requested by the Safety Monitor. All panic alerts for blinded values will be sent to the Safety Monitor and evaluated in real time.

12.1.11 Fresh biopsies

At selected US sites only: Optional lesional (if available) and nonlesional skin biopsy samples will be collected at selected sites for exploratory analysis at baseline/predose on Day 1 and post-dose at either Day 57, Day 71, or Day 85 during the double-blind period. These fresh biopsies will be shipped overnight to the Sponsor for additional cell phenotyping and other exploratory analysis. Once the Sponsor receives the biopsies, they will be dissociated into single cells and immunophenotyped for immune cell populations (lymphocytes, eosinophils, basophils, mast cells, neutrophils, and macrophages) and other exploratory analysis. Detailed instructions on collection, packaging and shipping will be included in the lab manual. All materials required for shipment of the additional samples will be provided to the site by the Central Laboratory.

12.2 Safety-Related Procedures

12.2.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at screening and at study visits if changes are made. Dose, route, unit, frequency of administration, indication for administration, and dates of medication will be captured. Any prior medication received within 30 days before screening and during the study through Day 155 or 84 (±5) days after last dose of

study drug, if ET, or through the first dose of study drug if the subject enters the OLE period of the study will be recorded.

For subjects participating in the OLE period, concomitant medications should be recorded in the AK002-027 double-blind treatment period database up until the first OLE dose is administered after the Day 85 (OLE Dose 1) visit. Rescue medications and procedures must be documented as rescue treatment in the source documents and on the Prior and Concomitant Medications eCRF.

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

12.2.2 Complete Physical Examination

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

12.2.3 Body Weight and Height

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

12.2.4 Symptom-Directed Physical Examination

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

12.2.5 Electrocardiogram

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

12.2.6 Previous CSU Diagnosis and Treatments Review

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

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

- For Inclusion Criteria #3, documentation of duration and a confirmed diagnosis of CSU should be supported by medical records and/or current documentation by the treating/study dermatologist (or allergist/immunologist) that the subject has a diagnosis of CSU which has been present for at least 6 months before screening based on patient interview.
- For Inclusion Criteria #4, the diagnosis of moderate-severe CSU refractory to H1-AH at a minimum of the licensed dose and at licensed frequency should be supported by treating/study dermatologist's (or allergist/immunologist) documented assessment at screening based on medical records or discussion with a referring physician.
- For Inclusion Criteria #6, the required stable dose of H1-AH between 1x and 4x of the licensed dose and at licensed frequency for treatment of CSU at least 1 week prior to screening needs to be confirmed by medical records and/or treating/study dermatologist's (or allergist/immunologist) notes.
- For Exclusion Criteria #3, the demonstrated lack of primary response to treatment with a biologic therapy (e.g. omalizumab) for the treatment of CSU should be confirmed by medical records and/or notes from the treating/study dermatologist (or allergist/immunologist).

More details are provided in the instructions on the eCRF pages and Study Reference Manual.

12.2.7 Vital Signs

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

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

Additional vital signs measurements may be collected at the Investigator's discretion if an IRR occurs. Vital signs including systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate will be measured after the subject has been at rest for ≥5 minutes and before any blood draws have been obtained (unless collected for an IRR). Please refer to the schedule of assessments in Table 1.

12.3 Clinical Laboratory Measurements

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

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

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

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

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

Therefore, a clinically significant lab value is one that indicates a new disease process, an exacerbation or worsening of an existing condition, or requires further action to be taken. For any laboratory test value outside the reference range that the Investigator considers clinically significant, the Investigator will:

- Repeat the test to verify the out-of-range value.
- Follow the out-of-range value to a satisfactory clinical resolution.

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

Blood will be obtained for CBC with differential as described in Section 12.1.10.

12.3.1 Blood Chemistry Profile

Blood for chemistry, including hCG and FSH (only for screening), will be collected. Subjects of childbearing potential and postmenopausal women are required to undergo serum hCG or FSH testing (as described in Section 12.3.2). Blood for chemistry will be obtained during screening, predose on all dosing days, as well as on follow-up days 85, 127, and 155 or 14, 56, and 84 (±5) days after last dose if ET.

The blood sample will be processed and shipped in accordance with the Laboratory Manual and laboratory kit instructions. A central laboratory will analyze the serum sample and provide results for chemistry tests including sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, creatine kinase, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), and lactate dehydrogenase.

12.3.2 Pregnancy Test and Follicle-Stimulating Hormone

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

Subjects with FSH levels ≤30 mIU/mL will be considered to be of childbearing potential. Blood will be collected for serum pregnancy test at screening. Urine will be collected for dipstick pregnancy test on all dosing days, Day 8, and all follow-up days (or 14, 56, and 84 (±5) days after last dose of study drug if ET) for all subjects of childbearing potential. Test kits will be supplied by the central laboratory. Tests will be completed on site and evaluated prior to each SC injection. If a subject has a positive pregnancy test, dosing will immediately be discontinued.

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

12.3.3 Effective Methods of Contraception for Allakos Studies

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

Applicable for Study Sites in the United States:

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

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

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

Barrier and other methods not listed above when used together as dual methods such as a condom + diaphragm or condom + spermicide are less effective methods. Therefore, these dual methods are not recommended as they could increase the risk of becoming pregnant during the

study or follow-up period. When using dual methods, at least 1 of the methods should be a highly effective method of contraception.

Applicable for Study Sites in Germany and Poland:

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

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]: Oral, intravaginal or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]: Oral, injectable, or implantable[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomised partner[2,3]
- Sexual abstinence[4]

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

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

12.3.4 Urinalysis

Urine will be obtained for urinalysis at screening and on follow-up Days 85 and 155 (14 and 84 [±5] days after last dose if ET), and symptom-based, as necessary. The urine sample will be processed and shipped in accordance with the Laboratory Manual and laboratory kit instructions. A central laboratory will analyze the urine sample for specific gravity, pH, protein, glucose, ketones, blood, and leukocyte esterase.

12.3.5 Serology

Blood will be obtained at screening for serology tests including hepatitis B surface antigen (HBsAG), hepatitis C antibody, hepatitis B core antibody (anti-HBc), and human immunodeficiency virus (HIV). The blood sample will be processed and shipped to the central laboratory in accordance with the Laboratory Manual and lab kit instructions. A positive result, if clinically significant (and not due to previous vaccination or resolved disease or exposure), will exclude the subject from enrollment (Appendix 8).

12.3.6 Anti-Lirentelimab Antibodies

Blood for determination of ADA will be collected predose on dosing Days 1, 29, and 43, and on follow-up Days 85 and 155 (14 and 84 [±5] days after last dose of study drug if ET) and on Day 8, between Dose 1 and Dose 2. The ADA sample will also be collected any time an immunogenicity-related AE occurs. Additional ADA samples will be collected at each dosing visit during the OLE period.

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

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

12.3.7 Blood for Pharmacokinetics

Blood samples for serum PK assessments will be collected predose on dosing Days 1, 15, 29, 43, 57, 71, and 85 (±5), on Day 8 (±3) between Dose 1 and Dose 2, and during follow-up on Days 85, 127, and 155 (±5) or 14, 56, and 84 (±5) days after last dose of study drug if ET. The serum samples will be collected predose and processed and shipped frozen in accordance with the study Laboratory Manual and lab kit instructions.

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

12.3.8 Blood for IgE

Blood will be collected for determination of serum IgE levels and sent to the central laboratory for processing. Blood will be collected during screening, predose on Day 43 and Day 71, and on follow-up Days 85, 127, and 155 or 14, 56, and 85 (±5) days after last dose of study drug if ET.

12.3.9 COVID-19 Testing

Testing for COVID-19 is not required for this study but may be implemented by the study site at any time during the study due to safety regulations or procedures. Testing for COVID-19 may be individually mandated by facilities or by state or country (e.g. Germany) regulation, and if required, this will be consented through the site and not listed in the AK002-027 ICF. Testing for COVID-19 may be performed according to the trial site standard procedures and safety regulations.

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

13. Evaluations and Procedures by Visit

Evaluations and procedures by visit are shown in Table 1.

General Information:

- All recorded clock times should utilize a 24-hour clock.
- Procedures for screening may be performed over the course of multiple visits prior to the first SC injection.
- Dose 1 is the day of the first SC injection. Dose 1/Day 1 can occur within a ±3 day window, i.e., the screening period can be a maximum of 17 days and a minimum of 11 days. Dosing visits must be conducted within the ± windows stipulated in the protocol with the following requirements:
  - The interval between dosing visits must be at least 7 days and no more than 21 days from the previous dosing visit unless directed otherwise by Allakos. The interval count starts the day after the visit and includes the day of the next visit.

  - The interval between the final dosing visit and the efficacy visit (Day 85) must be at least 11 days and no more than 17 days from the final dosing visit unless directed otherwise by Allakos. The interval count starts the day after the visit and includes the day of the next visit.

- For Day 8, the visit can occur within a ±3 day window.

13.1 Screening Day for H1-AH Dose Stabilization – Screening Period

~Day -21: For subjects entering screening without prior medication history of using a stable, approved dose of H1-AH for at least 7 days prior to Screening Day.

Day -14: For subjects meeting the definition of having a stable, approved dose of H1-AH, Screening Day will be Day -14.

1) Obtain written informed consent.
2) Assign the participant a PID.
3) Collect demographics.
4) Obtain medical history.
5) Gather and review CSU diagnosis and detailed previous treatment history and concomitant medications (Section 12.2.6).
6) Confirm H1-AH usage.
7) Collect body weight (in kg) and height (in cm)
8) Vital signs.
9) Perform ECG.
10) Conduct complete physical examination.
11) Administer [redacted].
12) Activate daily PRO and have subject complete first PRO (UPDD) in the clinic and have subject complete the [redacted] if subject has a history of [redacted].
13) Have subject complete the [redacted].
14) Collect blood for serology, serum IgE, chemistry (including hCG and FSH, if applicable), and CBC. Female subjects of childbearing potential are required to have serum hCG measured. Postmenopausal subjects are required to have serum FSH measured and if FSH level is ≤30 mIU/mL, a serum hCG measurement will be required during the screening period.

15) Collect urine for urinalysis.

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

13.2 Screening Day or Post H1-A1 Stabilization – Screening Period ~Day -14

1) Obtain written informed consent.

2) Assign the participant a PID.

3) Collect demographics.

4) Obtain medical history.

5) Gather and review CSU diagnosis and detailed previous treatment history and concomitant medications (Section 12.2.6).

6) Confirm H1-AH usage.

7) Collect body weight (in kg) and height (in cm)

8) Vital signs.

9) Perform ECG.

10) Conduct complete physical examination.

11) Administer [redacted].

12) Activate daily PRO and have subject complete first PRO (UPDD) in the clinic and have subject complete the [redacted] if subject has a history of [redacted].

13) Have subject complete the [redacted].

14) Collect blood for serology, serum IgE, chemistry (including hCG and FSH, if applicable), and CBC.

15) Collect urine for urinalysis.

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

17) SAE review, reporting of SAE occurring after signing the ICF and prior to the first SC injection, will be limited to those that relate to screening procedures. The capture of all SAE and AE that are not related to screening procedures will begin at the time of first SC injection of study drug.

13.3 Day -7 (±3) – Screening Period/Baseline

Phone Visit:

1) Assess the subject for SAE related to screening procedures.
2) Assess UPDD and [redacted] (if applicable) compliance.
3) Confirm continuing eligibility.
4) Document any changes to medical history and concomitant medications.
5) Confirm H1-AH usage.
6) Perform UAS7 assessment.
7) Complete [redacted].

13.4 Day 1 (±3) – Randomization/Day 1/Baseline/Dose 1

1) Prior to SC Injection:
    a) Assess the subject for SAE related to screening procedures.
    b) Confirm continuing eligibility.
    c) Assess UPDD and [redacted] (if applicable) compliance. Subject should complete at least four daily PRO questionnaires during the seven days prior to Day 1.
    d) Document any changes to health status.
    e) Document any changes to medical history and concomitant medications.
    f) Perform urine dipstick pregnancy test if subject is of childbearing potential.
    g) Collect body weight (in kg).
    h) Perform symptom-directed physical exam, if needed.
    i) Complete UAS7 and [redacted].
    j) Have subject complete the [redacted] and Atopic Conditions Questionnaire.
    k) Collect blood for chemistry, PK, and ADA.
    l) Optional: collect skin biopsies (applicable for select US sites only).
2) Randomization:
    a) Prior to randomizing the subject in the IRT system, the Investigator will determine subject's UAS7 score and biologic-naïve vs biologic-exposed status. The study coordinator or designee will enter UAS7 score and biologic status into the IRT on Study Day 1 to stratify the subject.

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

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

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

5) Post-SC Injection:

a) Collect vital signs within 15 minutes of the end of the injection.

b) Collect blood for CBC with differential 1 hour (±15 minutes) after the end of the injection.

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

d) Collect vital signs just prior to discharge.

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

13.5 Day 8 (±3)

1) Assess the subject for AE and SAE.

2) Document any changes to concomitant medications.

3) Assess UPDD and [redacted] (if applicable) compliance.

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

5) Complete UAS7 assessment.

6) Have subject complete the [redacted].

7) Collect blood for PK and ADA.

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

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

13.6 Day 15 (±5) – Dose 2

1) Prior to SC Injection:
   a) Assess the subject for AE and SAE.
   b) Document any changes to concomitant medications.
   c) Assess UPDD and [redacted] (if applicable) compliance.
   d) Complete UAS7 assessment.
   e) Have subject complete [redacted].
   f) Collect body weight (in kg).
   g) Perform urine pregnancy test if subject is of childbearing potential.
   h) Collect vital signs 30 (±5) minutes prior to the start of the SC injection.
   i) Perform symptom-directed physical exam, as needed.
   j) Collect blood for CBC, chemistry, and PK.
   k) The study pharmacist will prepare study drug using dosage and kit number(s) provided by the IRT. See the Pharmacy Manual for detailed SC injection preparations.
2) SC Injection of Study Drug: Subcutaneous dosing (lirentelimab SC or placebo SC) comprises 1 SC injection administered in the front of the thigh with a 27-gauge needle. Maximum volume administered will be 2 mL. See the Pharmacy Manual for SC injection instructions.
3) Post-SC Injection:
   a) Collect vital signs within 15 minutes of the end of the SC injection.
   b) Collect CBC with differential 1 hour (±15 minutes) after the SC injection.
   c) Observe the subject for at least 1 hour after the SC injection. Collect vital signs just prior to discharge.

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

13.7 Day 29 (±5) – Dose 3

1) Prior to SC Injection:
   a) Assess the subject for AE and SAE.
   b) Document any changes to concomitant medications.

c) Assess UPDD and [redacted] (if applicable) compliance.

d) Complete UAS7 and [redacted] assessments.

e) Have subject complete [redacted].

f) Collect body weight (in kg).

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

h) Collect vital signs 30 (±5) minutes prior to the start of the SC injection.

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

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

k) The study pharmacist will prepare study drug using dosage and kit number(s) provided by the IRT. See the Pharmacy Manual for detailed SC injection preparations.

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

3) Post-SC Injection:

a) Collect vital signs within 15 minutes of the end of the SC injection.

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

c) Observe the subject for at least 1 hour after the SC injection. Collect vital signs just prior to discharge.

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

13.8 Day 43 (±5) – Dose 4

1) Prior to SC Injection:

a) Assess the subject for AE and SAE.

b) Document any changes to concomitant medications.

c) Assess UPDD and [redacted] (if applicable) compliance.

d) Complete UAS7 assessment.

e) Have subject complete [redacted].

f) Collect body weight (in kg).

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

h) Collect vital signs 30 (±5) minutes prior to the start of the SC injection.

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

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

k) Collect blood for total serum IgE.

l) The study pharmacist will prepare study drug using dosage and kit number(s) provided by the IRT.

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

3) Post-SC Injection:

a) Collect vital signs within 15 minutes of the end of the SC injection.

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

c) Observe the subject for at least 1 hour after the SC injection. Collect vital signs just prior to discharge.

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

13.9 Day 57 (±5) – Dose 5

1) Prior to SC Injection:

a) Assess the subject for AE and SAE.

b) Document any changes to concomitant medications.

c) Assess UPDD and [redacted] (if applicable) compliance.

d) Complete UAS7 and [redacted] assessments.

e) Have subject complete [redacted].

f) Collect body weight (in kg).

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

h) Collect vital signs 30 (±5) minutes prior to the start of the SC injection.

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

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

k) The study pharmacist will prepare study drug using dosage and kit number(s) provided by the IRT.

l) Optional: collect skin biopsies on either Day 57, Day 71, or Day 85 (applicable for select US sites only).

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

3) Post-SC Injection:

a) Collect vital signs within 15 minutes of the end of the SC injection.

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

c) Observe the subject for at least 1 hour after the SC injection. Collect vital signs just prior to discharge.

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

13.10 Day 71 (±5) – Dose 6

1) Prior to SC Injection:

a) Assess the subject for AE and SAE.

b) Document any changes to concomitant medications.

c) Assess UPDD and [redacted] (if applicable) compliance.

d) Complete UAS7 assessment.

e) Have subject complete [redacted].

f) Collect body weight (in kg).

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

h) Collect vital signs 30 (±5) minutes prior to the start of the SC injection.

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

j) Collect blood for CBC, chemistry and PK.

k) Collect blood for total serum IgE.

l) The study pharmacist will prepare study drug using dosage and kit number(s) provided by the IRT.

m) Optional: collect skin biopsies on either Day 57, Day 71, or Day 85 (applicable for select US sites only).

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

3) Post-SC Injection:

a) Collect vital signs within 15 minutes of the end of the SC injection.

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

c) Observe the subject for at least 1 hour after the SC injection. Collect vital signs just prior to discharge.

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

13.11 Day 85 (±5) or 14 Days Post-Dose – Follow-up Visit 1

1) Assess the subject for AE and SAE.

2) Document any changes to concomitant medications.

3) Assess UPDD and [redacted] (if applicable) compliance.

4) Perform UAS7 and [redacted] assessments.

5) Have subject complete [redacted] and Atopic Conditions Questionnaire.

6) Collect body weight (in kg).

7) Collect urine for urinalysis.

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

9) Collect vital signs.

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

11) Collect blood for CBC, chemistry, PK, and ADA.
12) Collect blood for total serum IgE.
13) Optional: collect skin biopsies on either Day 57, Day 71, or Day 85 (applicable for select US sites only).

If the subject elects to receive OLE dosing, the OLE period of the study may begin after all Day 85 assessments of the double-blind period have been completed. The start of OLE dosing may be delayed for up to 7 days after completion of the Day 85 visit. The subject is in the double-blind period of the study until the first OLE dose of lirentelimab is administered.

13.12 Day 127 (±5) or 56 Days Post-Dose – Follow-up Visit 2

1) Assess the subject for AE and SAE.
2) Document any changes to concomitant medications.
3) Assess UPDD and [redacted] (if applicable) compliance.
4) Perform UAS7 and [redacted] assessments.
5) Have subject complete [redacted].
6) Collect body weight (in kg).
7) Perform urine pregnancy test if subject is of childbearing potential.
8) Collect vital signs.
9) Perform symptom-directed physical exam, as needed.
10) Collect blood for CBC, chemistry, and PK.
11) Collect blood for total serum IgE.

13.13 Day 155 (±5) or 84 Days Post-Dose – Follow-up Visit 3

1) Assess the subject for AE and SAE.
2) Document any changes to concomitant medications.
3) Assess UPDD and [redacted] (if applicable) compliance.
4) Perform UAS7 and [redacted] assessments.
5) Have subject complete [redacted].
6) Collect body weight (in kg).
7) Collect urine for urinalysis.
8) Perform urine pregnancy test if subject is of childbearing potential.

9) Collect vital signs.

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

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

12) Collect blood for total serum IgE.

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

13.14 End of Study Definition

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

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

The enrollment of the last subject in the double-blind period of the study is anticipated to occur in 2023. The last subject's last follow up visit will be approximately 24 weeks after the date of enrollment if OLE is not elected, or up to 36 weeks after the date of enrollment if the OLE is elected.

Please refer to Section 14.12 for the study ending prematurely.

14. Adverse Event Reporting and Documentation

14.1 Adverse Events

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

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

Examples of an AE include:

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

The following examples are not considered AE:

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

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

For subjects participating in the OLE period, AE will be recorded in the CRF of the AK002-027 double-blind treatment period database up until the first administration of lirentelimab in the OLE period and recorded in the CRF of the AK002-027 OLE period database beginning from the time of first administration of lirentelimab ending at the time of study completion or ET of the OLE period.

14.2 Serious Adverse Events

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

- Death
- A life-threatening AE that places the subject at risk of death at the time of the event. It does not refer to an event that hypothetically might cause death if it were more severe.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant disability/incapacity.
- A congenital anomaly/birth defect occurring in the offspring of a study subject.

- Other important medical events may also be considered a SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent any of the outcomes listed above.

Serious adverse events will be assessed and recorded beginning after the first administration of study drug and ending at Day 155 (±5) or 84 (±5) days after last dose, unless the SAE is related to a screening procedure, in which case it will be captured from the date of informed consent.

14.3 Adverse Events of Special Interest

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

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

Adverse Events of Special Interest will be assessed beginning after the time of first administration of study drug and ending on Day 155 (±5) or 84 (±5) days after last dose. Any new AESI (or new information related to a previously reported AESI) must be recorded in the AE eCRF and designated as an "AE of special interest."

14.4 Injection-Related Reactions

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

- Flushing
- Chills
- Back or abdominal pain
- Chest discomfort or tightness
- Dizziness
- Nausea
- Vomiting
- Sweating
- Fever
- Urticaria

- Shortness of breath
- Headache
- Hypotension or hypertension
- Pruritus
- Bronchospasm

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

14.5 Injection Site Reactions

All AE considered by the Investigator ***to be related to the SC administration*** of the biological substance at the injection site and occurring within 24 hours of the start of the injection should be captured as 1 injection site reaction (ISR).

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

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

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

14.6 Anaphylaxis

A suspicion of anaphylaxis will be carefully monitored and treated according to standard of care. Emergency crash cart equipment and medications, including multiple doses of epinephrine, vasopressors, and bronchodilators, will be available at all times during the conduct of the study. To define anaphylactic reactions in a consistent and objective manner, all AE of suspected anaphylaxis will be evaluated using Sampson's Criteria for Anaphylaxis (Appendix 7). The assessment of an AE will be done pursuant to definitions set forth by ICH Good Clinical Practice (GCP) guidelines and applicable regulatory requirements.

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

14.7 Evaluating Adverse Events and Serious Adverse Events

14.7.1 Establishing Diagnosis

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., dysuria, urinary nitrites should be reported as a urinary tract infection). If the diagnosis is not known, individual signs and symptoms should be assessed and recorded in the AE eCRF as separate AE.

The Investigator (or qualified Subinvestigator) must assign the AE attributes listed in Table 5 (AE severity), Table 6 (relationship to study drug), and Table 7 (relationship to study procedure) and is responsible for ensuring this information is recorded in the source documentation.

14.7.2 Assessment of Intensity

Investigators will use their clinical judgment as well as the guidelines laid out in the NCI CTCAE (version 5.0 or most current version) tables to assess the intensity of each AE and SAE (Table 5 and Appendix 6).

Table 5 Adverse Event Severity per CTCAE

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

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

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

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

14.7.3 Assessment of Causality to Study Drug

The Investigator should use their clinical judgment as well as the guidelines in Table 6 to assess the relationship between study drug and AE.

Table 6 Adverse Event Relationship to Study Drug

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

14.7.4 Assessment of Causality to Study Procedure

The Investigator should use their clinical judgment as well as the guidelines in Table 7 to assess the relationship between study procedure and AE. Assessment of causality to study procedure should include causality to such items as blood draw (as appropriate), or other.

Table 7 Adverse Event Relationship to Study Procedure

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

14.7.5 Action Taken

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

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

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

14.7.6 Assessment of Outcome

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

14.8 Adverse Event Reporting Procedures

14.8.1 All Adverse Events

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

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

later. Serious adverse events considered related to screening procedures will be recorded in the AE eCRF starting on the date of informed consent. Whenever appropriate, the CTCAE (version 5.0 or most current version) should be utilized for naming common AE (Appendix 6).

For subjects participating in the OLE period, AE will be recorded in the CRF of the AK002-027 double-blind treatment period database until the first administration of lirentelimab in the OLE period and recorded in the CRF of the AK002-027 OLE period database beginning at the time of the first administration of lirentelimab.

14.8.2 Serious Adverse Event Reporting

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

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

Even when only minimal information is available for the initial SAE report, the Investigator should try to make a causality assessment, as the causality is used to determine the timing of regulatory reporting requirements. If the Investigator or designee is not available to sign the SAE report on initial submission, they should be contacted and their assessment documented on the SAE form (with a note stating signature is forthcoming). The Investigator **may change** their causality assessment based on follow-up information and submit an amended SAE report form.

All efforts will be made to obtain accurate and complete medical records for the SAE. All efforts to obtain information should be documented in the subject's source documents.

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

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

available, such as hospital discharge notes and subject medical records, the Investigator will be notified and provided with all relevant information.

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

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

SAE must be reported within 24 hours to:

Fax: +1-888-237-7475

Email: SAE@allakos.com

14.8.3 Pregnancy Reporting

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

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

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

Any congenital abnormalities noted at birth in the offspring of a subject who received lirentelimab will be reported as a SAE. If the subject received lirentelimab, the outcome of any pregnancy and the presence or absence of any congenital abnormality will be recorded in the source documentation and reported to the Medical Monitor and Sponsor via the pregnancy reporting form.

14.8.4 AESI Reporting

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

For subjects participating in the OLE period, AESI will be assessed and recorded in the CRF of the AK002-027 double-blind treatment period database up until the start of the first OLE injection after the Day 85 visit and recorded in the CRF of the AK002-027 OLE period database beginning from the start of the first OLE injection after the Day 99 visit.

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

14.9 Medical Monitoring

Medical Monitoring is provided by the Sponsor for medically related questions.

14.10 Independent Data Monitoring Committee

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

At the sole discretion of the Sponsor, a separate independent statistical review committee may be convened and tasked to assess if there is evidence of a beneficial clinical effect prior to unblinding of the double-blind portion of the AK002-027 study. The primary and relevant secondary endpoints will be evaluated for this purpose. The statistical review committee will not be tasked with any determination as to stopping the study early for efficacy or futility. Greater detail concerning the statistical review committee will be provided in a separate charter.

14.11 Study Withdrawal Criteria

Participation of a subject will be discontinued in the event that:

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

14.12 Study Stopping Rules

14.12.1 General

The study will be temporarily or permanently discontinued, and the DMC will convene for discussion of the case and for providing advice on study restart in the event of any of the following:

- An unexpected life-threatening AE that is confirmed to be related to treatment.
- A fatal AE that is confirmed to be related to treatment.
- Sponsor obtains new information leading to unfavorable risk-benefit judgment of the study drug.
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons.
- Discontinuation of development of the Sponsor's study drug.

The Sponsor reserves the right to close a trial site or terminate the trial at any time for any reason at the sole discretion of the Sponsor.

The Sponsor will notify all principal investigators outlining the reasons for the termination of the clinical trial. The Sponsor will provide principal investigators with instructions if assessments beyond the regular per protocol procedures should be necessary.

14.12.2 Additional Regional Stopping Rules

The study must be discontinued in the affected region in the event of any of the following events:

- Approval of the national competent authority or the Favorable Opinion/Approval of IEC/IRB for the conduct of the clinical trial is withdrawn.
- The required modification of the maximum insured sum is not possible following a negative change in the assessment of the benefit-risk ratio, if applicable.

Health Authorities and IEC/IRB will be informed about the discontinuation of the study in accordance with applicable regulations.

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

15. Discontinuation and Replacement of Subjects

15.1 Definition of Study Completion

A subject who completes visits through the Day 155 visit will be categorized as having completed the double-blind period of the study.

A subject who completes visits through the Day 85 visit and enters the OLE period of the study will be categorized as having completed the double-blind period of the study.

A subject who completes visits through the OLE Day 155 visit will be categorized as having completed the OLE period of the study.

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

15.2 Early Discontinuation of Study Drug

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

- Subject withdraws consent.
- An AE that in the opinion of the Investigator results in it being in the best interest of the subject to discontinue study treatment.
- Protocol deviation requiring discontinuation of study treatment.
- Participation in any other study during the duration of this study.

- Use of a non-permitted concomitant drug, which may adversely affect data interpretation in the opinion of the Medical Monitor.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration or treatment of either a psychiatric or physical (e.g., infectious disease) illness.

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

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

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

16. Statistical Methods and General Considerations

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

When appropriate, summary statistics of number of non-missing values, mean, median, standard deviation, minimum, and maximum will be computed for continuous variables and summary statistics of number and proportion will be computed for categorical variables.

Two-sided 95% CI will be provided for the mean and proportion. No formal statistical inferences will be made for safety parameters. Safety data will be summarized for each treatment group unless otherwise specified.

Baseline for all safety and efficacy endpoints is defined as the last observations before administration of the first dose of study drug, unless otherwise specified.

Subjects will be stratified at randomization based on omalizumab experience for the treatment of CSU (exposed vs. naïve) and UAS7 score (16–27 vs. 28–42).

16.1 Sample Size

A sample size of approximately 55 subjects per treatment group will provide >90% power to demonstrate a statistically significant difference between lirentelimab and placebo in achieving a reduction in UAS7. We hypothesized a mean difference of at least 8 between lirentelimab SC

and placebo SC, and a pooled standard deviation of 11. This calculation is based on results derived from the AK002-006 study and expected placebo response rates reported in previously published data in H1-AH refractory CSU.

Randomization of up to 130 subjects (approximately 65 subjects per treatment group) is driven by the powering calculations, the likely dropout rate of up to approximately 10%, and will further support the evaluation of the safety and tolerability of lirentelimab SC.

16.2 Analysis Populations

The **Safety population** is defined as all subjects who received study medication.

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

The **Per Protocol (PP) population** is defined as mITT subjects who have received all 6 injections of study drug and do not have major protocol deviations possibly interfering with the interpretation of efficacy and safety assessment. The study statistician and study team will review protocol deviations to identify subjects to be excluded from the PP population analysis.

The mITT population will be used for all efficacy analysis, and the PP population will be used to evaluate sensitivity of the primary endpoint and secondary endpoints.

16.3 Subject Disposition

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

16.4 Demographic and Baseline Characteristics

The following demographic and baseline variables will be summarized:

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

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

16.5 Study Drug Exposure

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

16.6 Efficacy Analysis

16.6.1 Primary Efficacy Endpoint Analysis

The primary endpoint will be analyzed by analysis of covariance (ANCOVA). The least square (LS) mean, standard error (SE), and 95% CI for each treatment group and for the between group difference will be derived from ANCOVA with treatment as a factor, baseline UAS7 (continuous), and omalizumab experience for the treatment of CSU (exposed vs. naïve) as covariates. Data on subjects who experience an ICE (i.e., exit the study prematurely or initiate prohibited or rescue medications) prior to the end of Week 12 will be set to missing. Missing data imputation method will be provided in the SAP.

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

16.6.2 Secondary Efficacy Endpoint Analysis

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

Change from baseline in continuous secondary outcomes measured at multiple post-baseline time points will be analyzed longitudinally using a mixed model. The model will include 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. The model variance-covariance matrix will be unstructured. However, if computation does not converge, the variance-covariance matrix will take the form of Toeplitz, AR(1), and compound symmetry, whichever converges first. The Kenward-Rogers approach for computing denominator degrees of freedom will be used to account appropriately for pooling of within-subject and between-subject variance estimates. The LS means and the 95% CI for the between-group difference will be estimated for each week.

16.6.3 Exploratory Analysis

The binary exploratory efficacy endpoints will be analyzed using the Cochran-Mantel-Haenszel test adjusted by the randomization stratification factors. All exploratory efficacy endpoints of continuous nature will utilize MMRM procedure as described above.

The following exploratory endpoints will be analyzed:

- Impact on subject's [redacted] based on change in [redacted] at Week 12 compared with baseline.
- Impact on subject's [redacted] at Week 12 and Week 22 assessed as proportion of subjects achieving [redacted].
- Impact on [redacted] at Week 12 and Week 22 assessed as proportion of subjects achieving [redacted].
- Impact on [redacted] at Week 12 and Week 22 assessed as proportion of subjects achieving [redacted]

16.7 Safety Analysis

Subject incidence of TEAE will be tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term, and by severity and treatment relationship. Serious TEAE and TEAE leading to study discontinuation will be listed with pertinent information. Change from baseline in laboratory tests will be summarized with descriptive statistics. Details will be provided in the SAP.

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

16.7.1 Treatment Emergent Adverse Events

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

- Overview of TEAE to include
  - Number (%) of subjects who reported at least 1 TEAE overall, by severity and by relationship
  - Number (%) of subjects who reported at least 1 serious TEAE
  - Number (%) of subjects who reported at least 1 TEAE leading to treatment discontinuation

  - Number (%) of subjects who reported at least 1 TEAE of special interest (TEAESI)

- TEAE by preferred term
- TEAE by SOC and preferred term
- TEAE by maximum severity, SOC, and preferred term
- TEAE by SOC and preferred term and relationship to study drug
- TEAE leading to withdrawal by SOC and preferred term
- Serious TEAE by SOC and preferred term
- TEAESI by SOC and preferred term

16.7.2 Anti-Drug Antibodies

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

16.7.3 Clinical Laboratory Assessments

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

16.7.4 Vital Signs

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

16.7.5 ECG

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

16.7.6 Physical Exam

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

16.7.7 Concomitant Medications

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

16.8 Subject Confidentiality

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

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

17. Data Collection, Retention, and Monitoring

17.1 Data Collection Instruments

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

17.2 Data Management Procedures

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

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

17.3 Data Quality Control and Reporting

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

17.4 Database Lock/Disclosure of Randomization Code

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

- A provisional database lock after all subjects complete the Day 85 visit to allow for the analysis of safety and efficacy through Day 85.
- A final database lock after all subjects complete the study to allow for the analysis of any safety data collected after Day 85.

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

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

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

17.5 Archiving of Data

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

17.6 Availability and Retention of Investigational Records

In accordance with 21 CFR 312.62(c), GCP-V § 13 (10), ICH GCP E6 (R2), and all other applicable regulatory requirements, all essential documents at the study site, the Sponsor's

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

- Financial agreements
- Regulatory documents
- Independent Ethics Committee (IEC)/IRB documents
- Drug Accountability documents
- Correspondence
- Medical Reports
- Subject Data
- Monitoring Visit Reports
- Sample CRF and CRF Guidelines

17.7 Monitoring

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

18. Administrative, Ethical, and Regulatory Considerations

The study will be conducted in a manner consistent with this protocol, the Declaration of Helsinki (1996 version), IRB/IEC (21 CFR 56 and/or ICH E6), and Obligations of Clinical Investigators (21 CFR 312 and/or ICH E6), Directive 2001/20/EC (April 4, 2001) as well as other applicable local and national regulations. The Sponsor, the Investigators, and all

subcontracted organizations involved in the study conduct must also comply with all applicable privacy regulations (e.g., HIPAA, GDPR). The study can be initiated only after obtaining competent authority approval and IRB and/or IEC favorable opinion. If the competent authority withdraws the CTA approval or if the IRB withdraws the favorable opinion on the CTA, the conduct of the study will be terminated immediately.

18.1 Protocol Amendments

An amendment must be agreed to in writing by Allakos Inc. and submitted to the health authority as an Investigational New Drug (IND) amendment. An amendment which is considered substantial according to the EC CT-1 guidelines, must be submitted for review to the competent authority and the responsible IEC/IRB and cannot be implemented without prior written competent authority approval and the IEC/IRB favorable opinion. Written approval of a protocol amendment is not required prior to implementation of changes to the protocol that eliminate immediate hazard to the subject; however, approval must be obtained as soon as possible thereafter. Each protocol amendment must also be signed by the Investigator.

18.2 Independent Ethics Committees/Institutional Review Boards

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

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

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

18.3 Informed Consent Form

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

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

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

18.4 Publications

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

18.5 Clinical Study Registration

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

18.6 Payment to Subjects

All subjects may be compensated for participating in this study in accordance with the payment amounts per study day stated in the subject's signed ICF approved by the IEC/IRB. In accordance with Section 4.8.3 ICH E6 (R2), financial compensation from the sponsor to participating subjects shall be limited to the reimbursement of any travel expenses incurred (Germany only). In Poland, no incentives of financial rewards may be given, except for

compensation for costs incurred. If the subject is discontinued from the study prior to the last study visit, the subject will be compensated for each completed study visit on a pro rata basis as stated in the subject's ICF.

Beginning with Dosing Day 1, subjects will be compensated for each completed week of daily questionnaires as long as at least 4 questionnaires per week are completed. Subjects may be reimbursed for expenses associated with attending study visits.

No additional compensation beyond what is stated in the ICF is permitted.

18.7 Investigator Responsibilities

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

1) Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights, or welfare of subjects.

2) Personally conduct or supervise the study.

3) Ensure that the requirements relating to obtaining informed consent and IEC/IRB review and approval meet country requirements.

4) Report to the Sponsor or designee any AE that occurs in the course of the study, in accordance with 21 CFR Part 312.64 and/or ICH Guideline E2A.

5) Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

6) Maintain adequate and accurate records in accordance with 21 CFR Part 312.62 and ICH Guideline E6 and to make those records available for inspection with the Sponsor (or designee).

7) Ensure that an IEC/IRB that complies with the requirements of 21 CFR Part 56 and ICH Guideline E6 as applicable will be responsible for initial and continuing review and approval of the clinical study.

8) Promptly report to the IEC/IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).

9) Seek IEC/IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the subjects.

10) Comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements listed in 21 CFR Part 312 and/or ICH Guideline E6.

19. References

Altrichter S, Staubach P, Pasha M, Singh B, Chang, A, Bernstein J, Rasmussen H, Siebenhaar F, Maurer M. An open-label, proof-of-concept study of lirentelimab for antihistamine-resistant chronic spontaneous and inducible urticaria. J Allergy Clin Immunol, 2022;149:1683-90.

Bochner B. Siglec-8 on human eosinophils and mast cells, and Siglec-F on murine eosinophils, are functionally related inhibitory receptors. Clin Exp Allergy 2009;39:317–24.

Clinical Trials Facilitation and Coordination Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials, version 1.1. 21 Sep 2020, accessed 28 Jun 2022, https://legemiddelverket.no/Documents/Godkjenning/Klinisk%20utpr%C3%B8ving/2014_09_HMA_CTFG_Contraception_guidance%20Version%201.1.pdf.

European Medicine Agency. 31/01/2023 Xolair – EMEA/H/C/00606 – N/0117. Xolair: EPAR – Product Information. 01 Feb 2023, accessed 15 Feb 2023, https://www.ema.europa.eu/en/medicines/human/EPAR/xolair.

Food and Drug Administration. Birth Control Chart from FDA.gov/consumers/free-publications-women/birth-control. 18 Jun 2021a, accessed 27 Feb 2022, https://www.fda.gov/consumers/free-publications-women/birth-control.

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

Garg A, Cranwell A, Chan D. Cetirizine – how much is too much? J Pharmacy Practice and Research. 2018;48:170-172.

Maurer M, Weller K, Bindslev-Jensen C, Gimenez-Arnau A, Bousquet P, Bousquet J, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA^{2}LEN task force report. Allergy, 2011;66:317–30.

Maurer M, Rosén K, Hsieh HJ, Saini S, Grattan C, Gimenéz-Arnau A, Agarwal S, Doyle R, Canvin J, Kaplan A, Casale T. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med. 2013;368:924-35.

Metz M, Maurer M. Omalizumab in chronic urticaria. Curr Opin Allergy Clin Immunol, 2012;12:406–11.

Metz M, Ohanyan T, Church M, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. J Dermatol Sci, 2014a;73:57–62.

Metz M, Ohanyan T, Church M, Maurer M. Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. JAMA Dermatol, 2014b;150(3):288–90.

Metz M, Vadasz Z, Kocatürk E, Giménez-Arnau A. Omalizumab updosing in chronic spontaneous urticaria: an overview of real-world evidence. Clin Rev Allergy Immunol, 2020;59:38–45.

Mlynek A, Magerl M, Hanna M, Lhachimi S, Baiardini I, Canonica G, et al. The German version of the Chronic Urticaria Quality-of-Life Questionnaire: factor analysis, validation, and initial clinical findings. Allergy, 2009;64:927–36.

Sampson H, Munoz-Furlong A, Campbell R, Adkinson Jr N, Bock S, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391–7.

Sanofi. Update on ongoing Dupixent® (dupilumab) chronic spontaneous urticaria Phase 3 program. 18 Feb 2022, accessed 16 Nov 2022, https://www.sanofi.com/en/media-room/press-releases/2022/2022-02-18-06-00-00-2387700.

Tashiro M, Sakurada Y, Iwabuchi K, Mochizuki H, Kato M, Aoki M, et al. Central effect of fexofenadine and cetirizine: measurement of psychomotor performance, subjective sleepiness, and brain histamine H1-receptor occupancy using 11C-doxepin positron emission tomography. J Clin Pharmacol, 2004;44:890-900.

Wertenteil S, Strunk A, Garg A. Prevalence estimates for chronic urticaria in the United States: A sex- and age-adjusted population analysis. J Am Acad Dermatol, 2019;81:152–56.

Zhao Z, Ji C, Yu W, Meng L, Hawro T, Wei J, Maurer M. Omalizumab for the treatment of chronic spontaneous urticaria: A meta-analysis of randomized clinical trials. J Allergy Clin Immunol, 2016;137:1742–50.e4.

Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica G, et al. The EAACI/GA^{2}LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy, 2014;69:868–87.

Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy, 2022;77:734-766.

20. Appendices

20.1 Appendix 1: Urticaria Patient Daily Diary – PRO for Itch and Hives Severity

20.2 Appendix 2: [redacted]

20.3 Appendix 3: [redacted]

20.4 Appendix 4: [redacted]

20.5 Appendix 5: Atopic Conditions Questionnaire

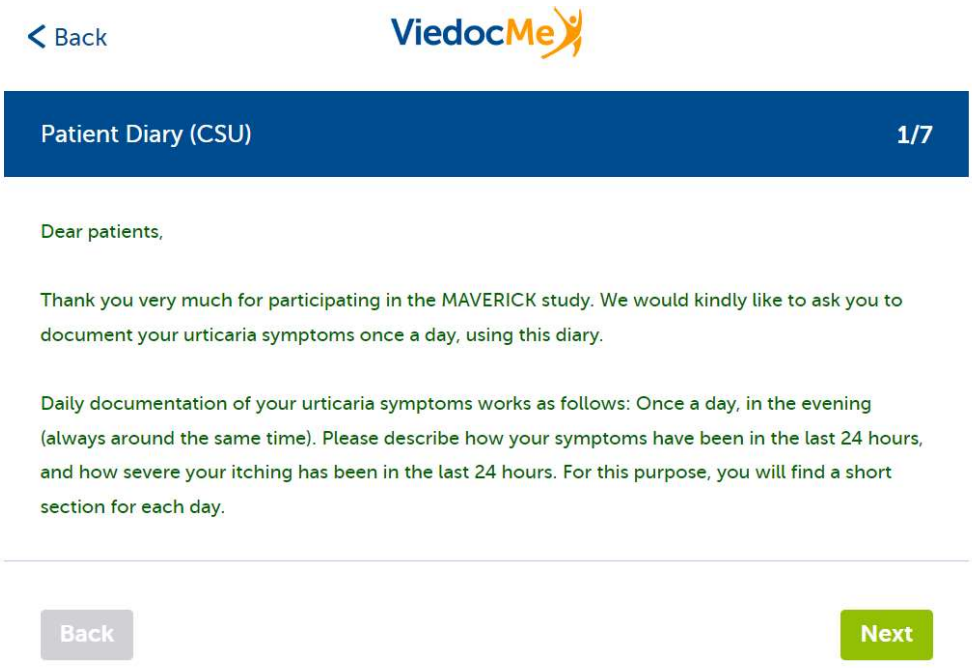
20.6 Appendix 6: Common Terminology Criteria for Adverse Events v. 5.0

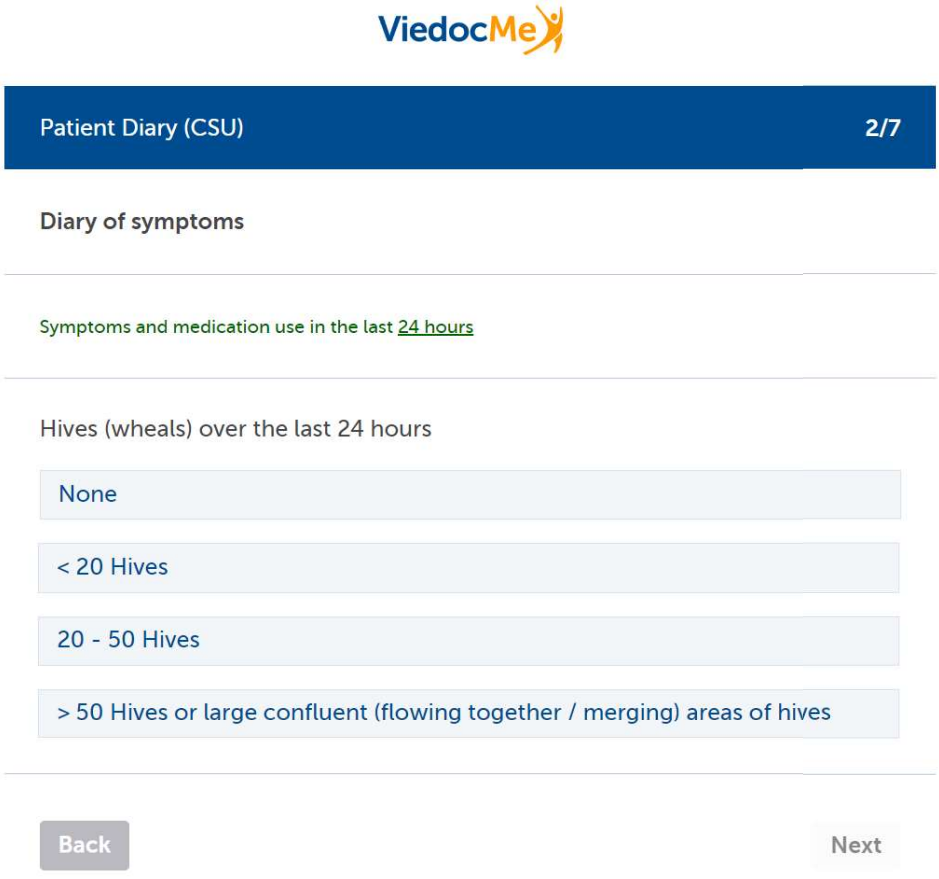
20.7 Appendix 7: Sampson's Criteria of Anaphylaxis

20.8 Appendix 8: Hepatitis B and Hepatitis C Serologic Testing Details

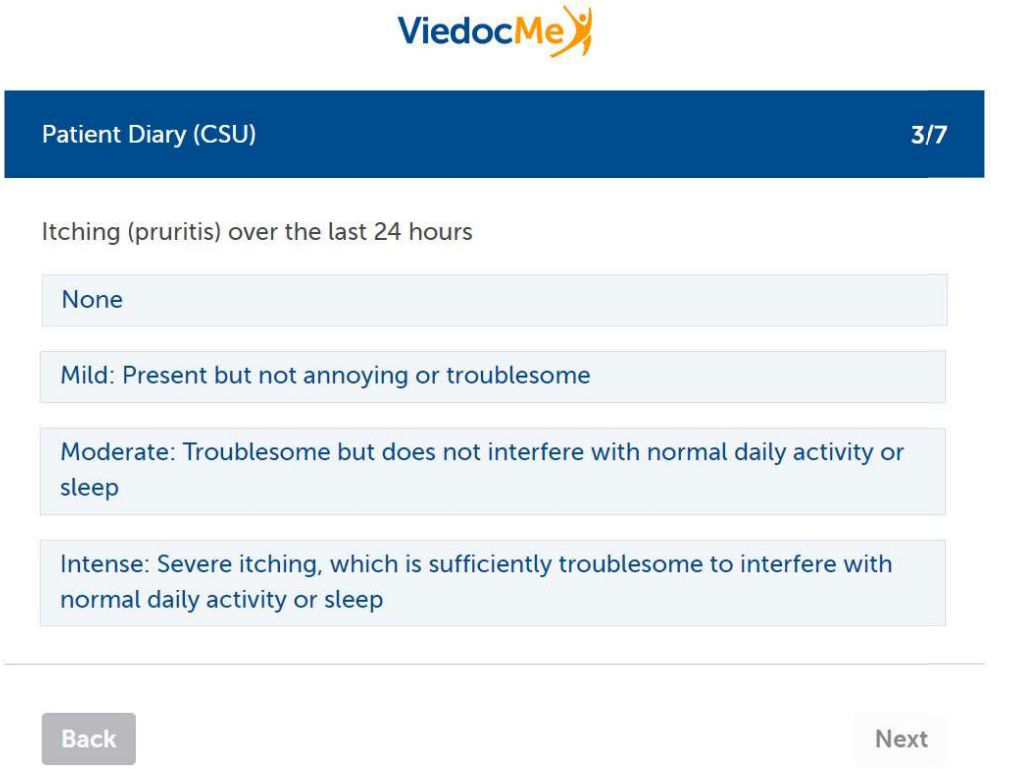
20.9 Appendix 9: Open Label Extension Period (Optional)

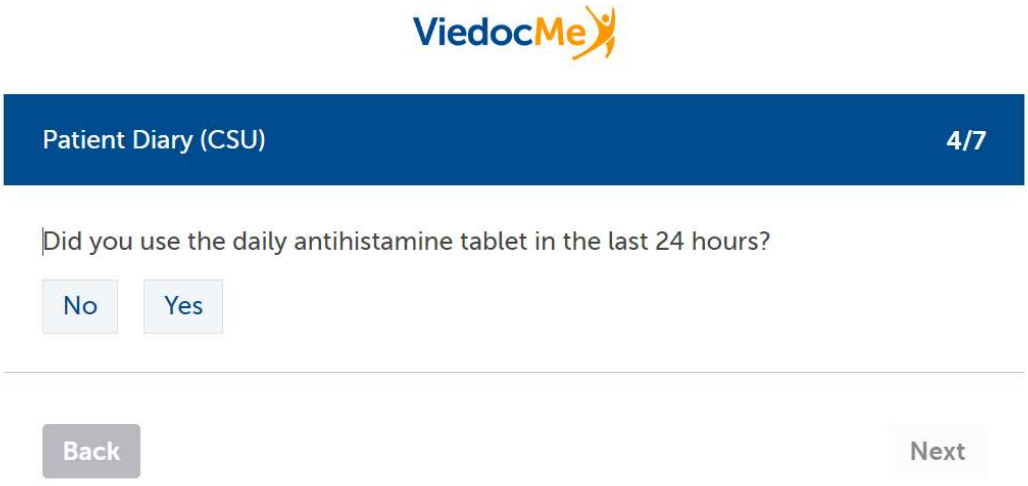
20.1 Appendix 1: Urticaria Patient Daily Diary – PRO for Itch and Hives Severity



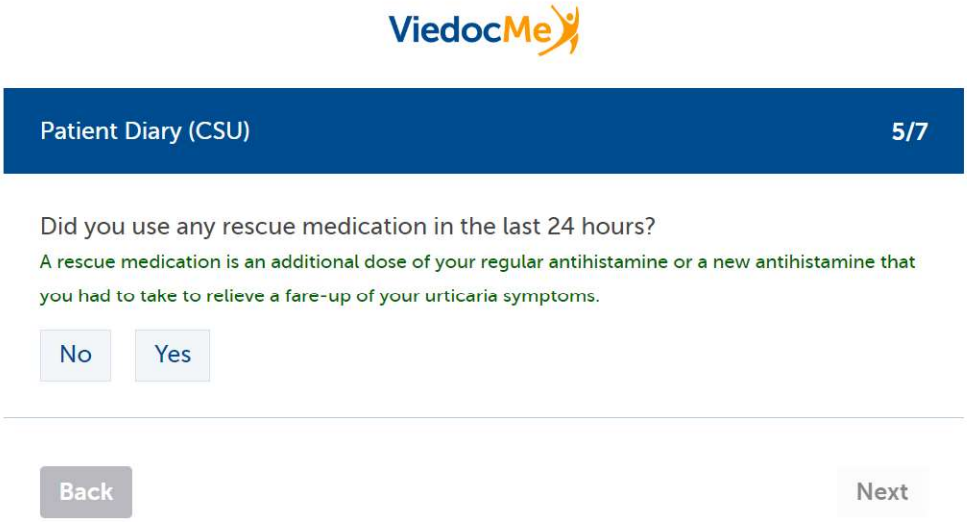


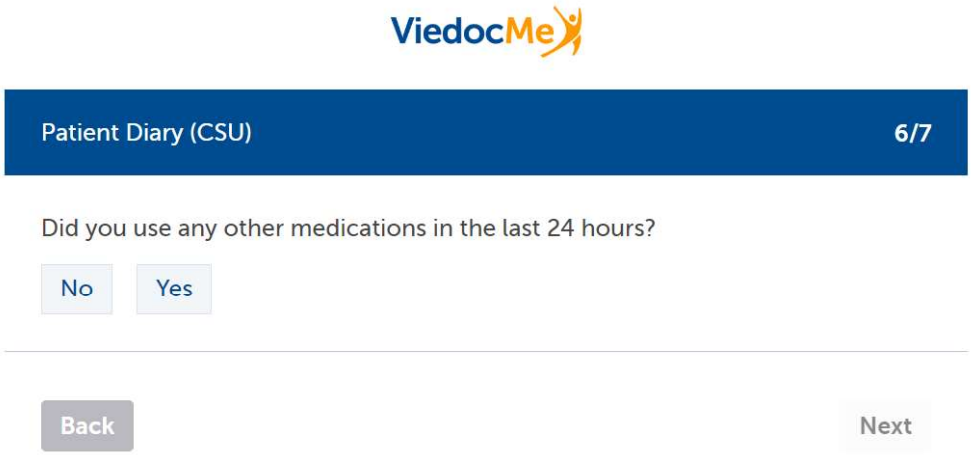
20.1 Appendix 1: Urticaria Patient Daily Diary – PRO for Itch and Hives Severity cont.





20.1 Appendix 1: Urticaria Patient Daily Diary – PRO for Itch and Hives Severity cont.





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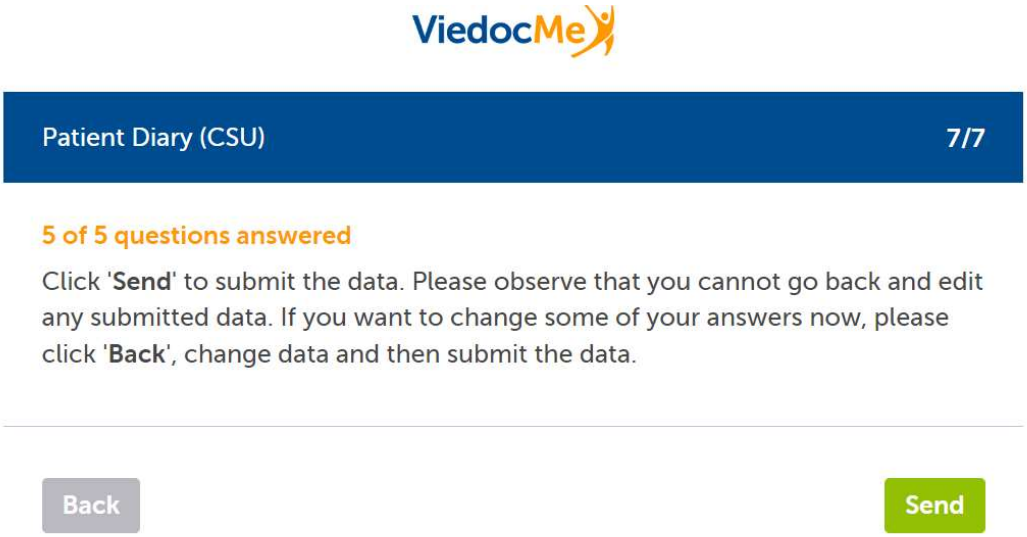


20.2 Appendix 2: [redacted]

[redacted]

20.2 Appendix 2: [redacted]

[redacted]

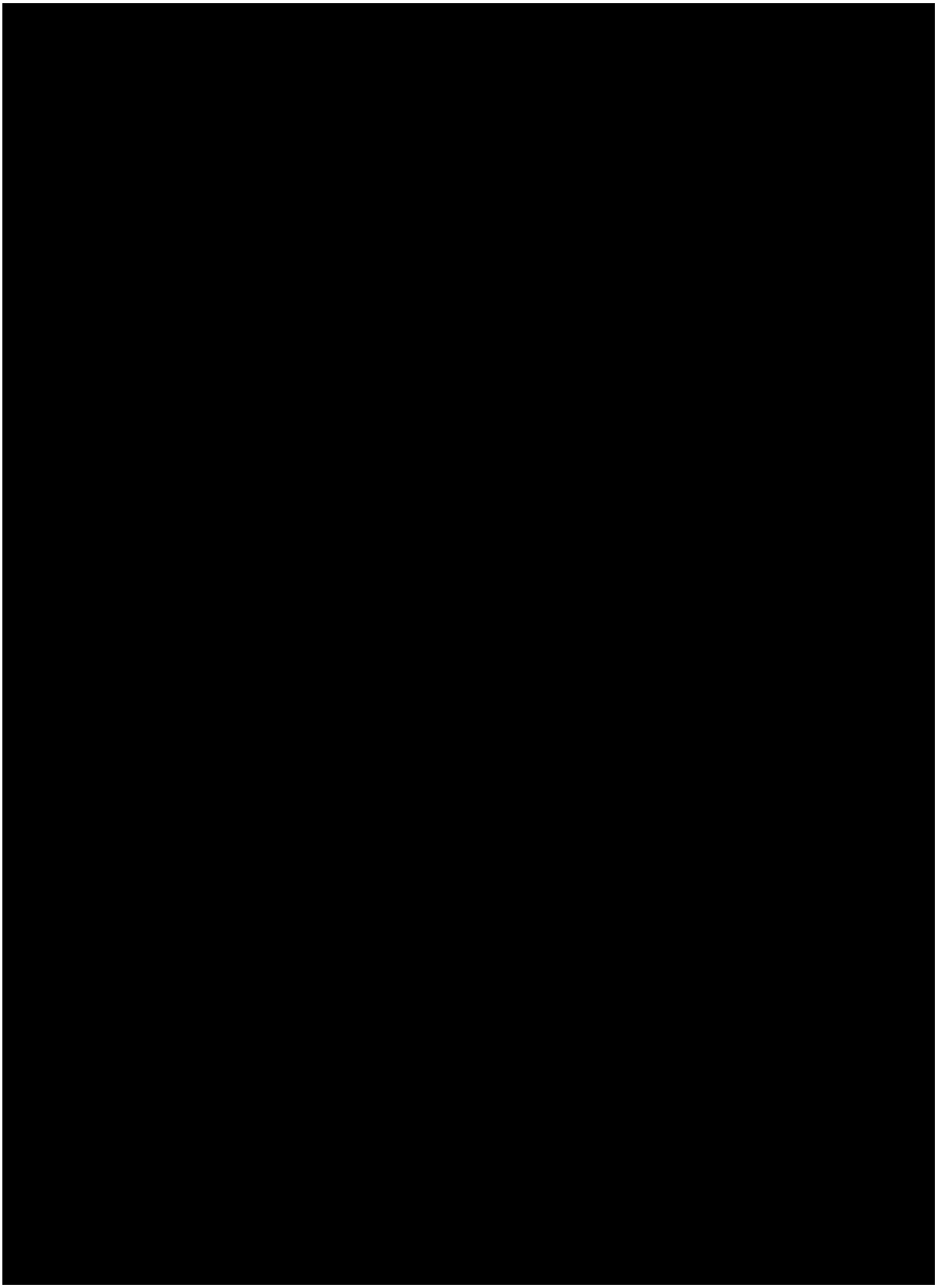
20.2 Appendix 2: [redacted]

[redacted]

20.2 Appendix 2: [redacted]

[redacted]

20.3 Appendix 3: [redacted]



20.4 Appendix 4: [redacted]

[redacted]

20.5 Appendix 5: Atopic Conditions Questionnaire

AK002-027 - Atopic Conditions Questionnaire **Patient Study ID: 227-_____-_____**

☐Day 1 ☐ Day 85 ☐OLE Day 1* ☐ OLE Day 85

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

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

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

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

*** Not applicable if OLE Day 1 takes place the same day as the Day 85 of the double-blind period.**

Patient signature **Date**

v. 10DEC2022

20.6 Appendix 6: Common Terminology Criteria for Adverse Events v. 5.0

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

http:\\ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Examples for grading of terms are shown below in Figure 4 Example of Grading for General Disorders and Administration Site Conditions and Figure 5 Example of Grading for Laboratory Abnormalities (Investigations).

General disorders and administration site conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypothermia	-	35 - >32 degrees C; 95 - >89.6 degrees F	32 - >28 degrees C; 89.6 - >82.4 degrees F	<=28 degrees C; 82.4 degrees F; life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Definition: A disorder characterized by an abnormally low body temperature. Treatment is required when the body temperature is 35C (95F) or below. **Navigational Note:** -					
Infusion site extravasation	Painless edema	Erythema with associated symptoms (e.g., edema, pain, induration, phlebitis)	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of the infusion into the surrounding tissue. Signs and symptoms may include induration, erythema, swelling, burning sensation and marked discomfort at the infusion site. **Navigational Note:** -					
Injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection. **Navigational Note:** -					
Localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation at a specific anatomic site. **Navigational Note:** Prior to using this term consider specific edema areas: General disorders and administration site conditions: Edema face, Edema limbs, Edema trunk, or Edema neck; Nervous system disorders: Edema cerebral; Reproductive system and breast disorders: Genital edema; Respiratory, thoracic and mediastinal disorders: Laryngeal edema or Pulmonary edema; Skin and subcutaneous tissue disorders: Periorbital edema; Vascular disorders: Lymphedema					
Malaise	Uneasiness or lack of well being	Uneasiness or lack of well being limiting instrumental ADL	Uneasiness or lack of well being limiting self-care ADL	-	-
Definition: A disorder characterized by a feeling of general discomfort or uneasiness, an out-of-sorts feeling. **Navigational Note:** -					
Multi-organ failure	-	-	Shock with azotemia and acid-base disturbances; significant coagulation abnormalities	Life-threatening consequences (e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis)	Death
Definition: A disorder characterized by progressive deterioration of the lungs, liver, kidney and clotting mechanisms. **Navigational Note:** -					

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Figure 4 Example of Grading for General Disorders and Administration Site Conditions

20.6 Appendix 6: Common Terminology Criteria for Adverse Events v. 5.0 cont.

Investigations					
CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-
Definition: A finding based on laboratory test results that indicate an increase in the level of lipase in a biological specimen. **Navigational Note:** -					
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen. **Navigational Note:** -					
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow. **Navigational Note:** -					
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen. **Navigational Note:** -					
Pancreatic enzymes decreased	<LLN and asymptomatic	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of pancreatic enzymes in a biological specimen. **Navigational Note:** -					
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen. **Navigational Note:** -					
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-
Definition: A finding based on laboratory test results that indicate an increase in the levels of amylase in a serum specimen. **Navigational Note:** -					
Thyroid stimulating hormone increased	TSH increased and no intervention initiated	-	-	-	-
Definition: A disorder characterized by an increase in thyroid stimulating hormone. **Navigational Note:** If intervention initiated or symptomatic, report as Endocrine disorders: Hypothyroidism.					

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Figure 5 Example of Grading for Laboratory Abnormalities (Investigations)

20.7 Appendix 7: Sampson's Criteria of Anaphylaxis

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

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

OR

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

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

20.8 Appendix 8: Hepatitis B and Hepatitis C Serologic Testing Details

Hepatitis B Testing Details

HBsAg positive subjects are excluded. However, in case of past infections/vaccinations in order to qualify, the subject's testing status needs to align with the information in Table 8.

Table 8 Hepatitis B Testing

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

Hepatitis C Testing Details

Anti-HCV positive and HCV-RNA positive are excluded. In order to qualify for enrollment, the subject's testing status needs to align with the information in Table 9.

Table 9 Hepatitis C Testing

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

20.9 Appendix 9: Open Label Extension Period (Optional)

20.9.1 Summary of the Open-Label Extended Dosing Period

Subjects who complete the double-blind, placebo-controlled treatment period (including the Day 85 study visit) and meet the open-label extended dosing eligibility criteria will be given the option to receive 6 doses of 300 mg lirentelimab SC through the open-label extension (OLE) dosing period.

On Day 85 (±5 days) of the double-blind period, eligible subjects participating in the OLE period will begin following the OLE Schedule of Assessments (Table 10) and will no longer follow the Double-Blind Period Schedule of Assessments (Table 1). The subjects starting the OLE period on Day 85 of the double-blind period do not need to repeat any assessments that overlap with Day 85 from the double-blind period.

The OLE dosing period is summarized as follows:

- The Investigator will evaluate whether the subject is eligible for OLE. If eligible, the subject will be given the option to participate in the OLE period and receive 6 doses of open-label 300 mg lirentelimab SC administered every 2 weeks starting on Day 85 of the double-blind period, which will be considered Day 1 of the OLE period. OLE dosing may be delayed for up to 7 days after completion of the Day 85 visit.
- On Day 85, eligible subjects who choose to participate in the OLE period will begin following the OLE Schedule of Events (Table 10). Subjects starting the OLE period on Day 85 of the double-blind period do not need to repeat any assessments that overlap with Day 85 from the double-blind period.
- Day 1 of the OLE can occur up to 7 days following Day 85 of the double-blind period. In case Day 1 of the OLE is not the same as Day 85 of the double-blind period, applicable subjects (women of childbearing potential) will have to take a urine dipstick pregnancy test.
- Subsequent doses will be given on OLE Days 15, 29, 43, 57, and 71 (±5 days).
- All differential blood counts will be blinded to the Sponsor and the site until after OLE Day 1 dosing.
- Subjects will remain at the site for at least 1 hour of observation after each dose. In the event of an IRR, the subject may require prolonged observation (>1 hour or until the symptoms resolve), as per Investigator discretion.

- Subjects will be followed for approximately 12 weeks after the last dose. Follow-up visits will occur on OLE Days 85, 127, and 155 (14, 56, and 84 [±5] days) after the last dose of open-label study drug.
- If absolute lymphocyte and/or eosinophil counts have not recovered by the OLE Day 155 visit (last follow-up visit), subjects will return approximately every 28 days for extended follow-up until counts have recovered.
- If extended follow-up is required, data collection will be limited to hematology, SAE, and AESI.

20.9.2 OLE Objective

The objective of the OLE period is to evaluate long-term safety and tolerability of up to 6 doses of open-label lirentelimab in subjects with CSU. The Medical Monitor will review data from the OLE period relating to safety and tolerability throughout the course of OLE dosing.

20.9.3 OLE Eligibility Criteria

Following completion of the randomized, double-blind, placebo-controlled treatment period (including the Day 85 visit), eligible subjects will have the option to receive 6 doses of open-label 300 mg lirentelimab SC through participation in the OLE period.

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

20.9.4 OLE Inclusion Criteria

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

1) Subject completed the randomized, double-blind, placebo-controlled treatment period and the Day 85 visit procedures.

2) Subject is willing and able to comply with the OLE period Schedule of Events (Table 10), including receiving the first open-label 300 mg lirentelimab SC at the Day 85 visit which is 14 days following the last dose of study drug in the double-blind period. OLE dosing may be delayed for up to 7 days after completion of the Day 85 visit.

3) Subject demonstrates continued eligibility per applicable inclusion criteria (Section 8.4) and exclusion criteria (Section 8.5) of the protocol. “Screening” in Section 13.1 and Section 13.2. refers only to the screening period completed prior to enrollment in the double-blind treatment period of the study and is not applicable to the OLE period.

20.9.5 OLE Exclusion Criteria

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

1) Previous administration of the study drug (lirentelimab or placebo) was poorly tolerated by the subject, in the opinion of the Investigator.
2) Any other reason that in the opinion of the Investigator or Medical Monitor makes the subject unsuitable for participation in the OLE period.

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

20.9.6 OLE Treatment

Formulation, storage, preparation, and administration of the open-label lirentelimab SC for the OLE will be consistent with Section 10 of the protocol and the AK002-027 Pharmacy Manual.

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

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

20.9.7 OLE Procedures and Guidelines

The OLE period will be conducted in accordance with Table 10 (Schedule of Assessments: Open-Label Extension Period) and the protocol. This includes prohibited medications, dietary and lifestyle restrictions, study drug preparation and administration, study assessment and procedure guidelines, AE reporting, withdrawal criteria and stopping rules, data collection and management, and ethical and regulatory requirements.

The Investigator will evaluate whether the subject is eligible for the OLE period. On Day 85, eligible subjects that choose to participate in the OLE period will begin following the OLE Schedule of Assessments (Table 10) and will receive the first open-label dose of lirentelimab.

Table 10 Study AK002-027 Schedule of Assessments: Open-Label Extension Period

Assessment/Procedure Description	OLE Treatment Period (12 weeks)						OLE Follow-Up Period (12 weeks)		
	OLE Day 1[16] (±5 days) OLE Baseline (Day 85-DB)[16]	**OLE Day 15** (±5 days)	**OLE Day 29** (±5 days)	**OLE Day 43** (±5 days)	**OLE Day 57** (±5 days)	**OLE Day 71** (±5 days)	**OLE Day 85** (±5 days)	**OLE Day 127** (±5 days)	**OLE Day 155** (±5 days)
	Week 12 **OLE Dose 1**	Week 14 **OLE Dose 2**	Week 16 **OLE Dose 3**	Week 18 **OLE Dose 4**	Week 20 **OLE Dose 5**	Week 22 **OLE Dose 6**	Week 24 **FUP-1**	Week 30 **FUP-2**	Week 34 **FUP-3/EOS**
Confirm informed consent for OLE	X								
Prior/concomitant medications	X	X	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X	X	X
Vital signs[1]	X	X	X	X	X	X	X	X	X
Symptom-directed physical exam[2]	X	X	X	X	X	X	X	X	X
UPDD[3]	<----------Complete daily from screening through OLE Day 155 or 84 days post-last dose---------->								
UAS7[4]	X	X	X	X	X	X	X	X	X
[redacted][5]	X		X		X		X	X	X
[redacted][6] (if applicable)	X	X	X	X	X	X	X	X	X
[redacted]	X	X	X	X	X	X	X	X	X
Atopic Conditions Questionnaire[7]	X						X		
Blood for total serum IgE[8]	X			X		X	X	X	X
Blood for chemistry[9]	X	X	X	X	X	X	X	X	X
Blood for CBC with differential[10]	X	X	X	X	X	X	X	X	X
Blood for PK[11]	X	X	X	X	X	X	X	X	X
Blood for ADA[12]	X			X			X		X
Urine for dipstick pregnancy[13]	X	X	X	X	X	X	X	X	X
Urine for urinalysis[14]	X						X		X

Assessment/Procedure Description	OLE Treatment Period (12 weeks)						OLE Follow-Up Period (12 weeks)		
	OLE Day 1[16] (±5 days) OLE Baseline (Day 85-DB)[16]	**OLE Day 15** (±5 days)	**OLE Day 29** (±5 days)	**OLE Day 43** (±5 days)	**OLE Day 57** (±5 days)	**OLE Day 71** (±5 days)	**OLE Day 85** (±5 days)	**OLE Day 127** (±5 days)	**OLE Day 155** (±5 days)
	Week 12 **OLE Dose 1**	Week 14 **OLE Dose 2**	Week 16 **OLE Dose 3**	Week 18 **OLE Dose 4**	Week 20 **OLE Dose 5**	Week 22 **OLE Dose 6**	Week 24 **FUP-1**	Week 30 **FUP-2**	Week 34 **FUP-3/EOS**
Eligibility assessment	X								
Study drug administration	X	X	X	X	X	X			
Non-serious adverse events[15]	X	X	X	X	X	X	X	X	X
Serious adverse events[15]	X	X	X	X	X	X	X	X	X

ADA: Anti-lirentelimab antibody [redacted]

AAS: Angioedema Activity Score

CBC: Complete Blood Count

DB: Double-Blind

EOS: End of Study

FSH: Follicle-Stimulating Hormone

FUP: Follow-up

hCG: Human Chorionic Gonadotropin

UAS7: Weekly Urticaria Activity Score

[redacted]

UPDD: Urticaria Patient Daily Diary

Table 10 Notes

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

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

3) All subjects will be provided with the UPDD and will receive clear instructions on the completion of the UPDD. The UPDD includes UAS7 (itch and hives) for CSU subjects for clinical symptoms and activity interference.

4) The UAS7 is the sum for 7 days of the daily HSS and the daily ISS based on information collected in the UPDD and will be assessed weekly.

5) The [redacted] is a [redacted] questionnaire for assessing [redacted] and will be administered to the subject when in clinic.

Table 10 Notes cont.

6) The [redacted] will be completed by those subjects that also have a history of [redacted] at screening.

7) Subjects will be prompted to answer additional questions about symptoms related to asthma, allergic rhinitis, and allergic conjunctivitis.

8) Blood samples for total serum IgE will be collected predose on OLE Days 1, 43, and 71, on follow-up OLE Days 85, 127, and 155, or 14, 56, and 84 (±5) days after the last dose of study drug if ET.

9) Blood for chemistry, including hCG, will be collected. Only subjects of childbearing potential and postmenopausal women are required to have hCG testing completed. Blood for chemistry will be obtained predose on all dosing days and on all follow-up days (14, 56, and 84 [±5] days after the last dose of study drug if ET).

10) Blood for CBC with differential, including absolute blood eosinophil count, will be obtained just prior to each SC injection, 1 hour (±15 minutes) after the end of each SC injection, and on all follow-up days (14, 56, and 84 [±5] days after last dose if ET). An unscheduled CBC may be collected at the request of the Safety Monitor.

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

12) Blood for ADA will be collected predose on Days 1 and 43 and on follow-up Days 85 and 155 (14 and 84 [±5] days after last dose of study drug if ET). The ADA sample will also be collected any time an immunogenicity-related AE occurs.

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

14) Urine for standard urinalysis will be obtained at OLE Dose 1 and on follow-up OLE Days 85 and 155 (14 and 84 days [±5] if ET), and symptom-based, as necessary.

15) The capture of non-serious AE, SAE, and AESI will continue throughout the open-label period.

16) If OLE Day 1 takes place the same day as Day 85, the following assessments should only be done under Day 85 and not duplicated under OLE Day 1: prior/concomitant medications, body weight, symptom-directed physical exam (if applicable), UPDD, USA7, [redacted] Atopic Conditions Questionnaire, blood for IgE, chemistry, CBC, PK, and ADA, urine for dipstick pregnancy test (if applicable), and non-serious and serious adverse events. Blood draw and vital sign assessments must follow OLE Schedule of Events (as per above table notes).