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

NCT Number: NCT05528861

Document Date: 03 November 2023

Statistical Analysis Plan for Protocol AK002-027

Protocol 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
Protocol Number	AK002-027
Protocol Version	Amendment 3 07 September 2023 (Global) Amendment 4 23 September 2023 (US Only)
Study Drug	AK002 (lirentelimab)
Study Phase	2
IND Number	157566
Sponsor	Allakos Inc., 825 Industrial Road, Suite 500, San Carlos, CA 94070 USA
SAP Version	1
SAP Date	03 November 2023

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List of Abbreviations

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

MMRM	Mixed Model for Repeated Measures
NRI	Nonresponder Imputation
OLE	Open-label extension
p-value	Probability value
PD	Pharmacodynamics
PE	Physical examination
PK	Pharmacokinetic(s)
PP	Per protocol population
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical analysis system
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SDTM	Study Data Tabulation Model
SOC	System organ class
TEAE	Treatment-emergent adverse event(s)
TEAESI	Treatment-emergent adverse event(s) of special interest
TESAE	Treatment-emergent serious adverse event(s)
TLF	Tables, listings, and figures
[redacted]	[redacted]
ULN	Upper limit of normal
UPDD	Urticaria Patient Daily Diary
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

Revision History

Version Date	Version Number	Brief Summary of Changes
03 November 2023	Version 1	Original document

1. Introduction

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of lirentelimab administered via subcutaneous injection (SC) in omalizumab-naïve or exposed adult subjects with H1-antihistamine (H1-AH) refractory chronic spontaneous urticaria (CSU).

The statistical analysis plan (SAP) describes *a priori* the data and variables to be summarized or analyzed, including specifications of the analytical methods to be performed. This SAP supersedes the statistical analysis methods described in the clinical protocol except for the standard pharmacokinetic (PK) data analyses. Significant deviations/changes from the planned analyses described in this SAP will be identified, with justification, in the appropriate section of the clinical study report (CSR). The SAP is based on Clinical Study Protocol AK002-027 Amendment 3, dated 07 September 2023 (Global), Clinical Study Protocol AK002-027 Amendment 4, dated 23 September 2023 (US Only), and the associated electronic case report form (eCRF).

2. Study Objectives

2.1 Primary Objective and Endpoint

The primary objective of the study is to assess the efficacy of lirentelimab SC in adult subjects with CSU.

The associated estimand for this objective is the effect of therapy with lirentelimab SC as assessed by the absolute change in weekly Urticaria Assessment Score (UAS7) from baseline to Week 12.

2.1.1 Weekly Urticaria Assessment Score (UAS7)

The UAS7 is the sum for 7 days of the daily Hives Severity Score (HSS) and the daily Itch Severity Score (ISS). 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.

The severity of hives will be recorded by all subjects once daily in their Urticaria Patient Daily Diary (UPDD), on a scale of 0 (none) to 3 (> 50 hives) (see Table 1). A weekly HSS score (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. Missing data will be imputed using methods outlined in Section 6.9.1. 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 1 Hives Severity Score

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

The severity of itching will be recorded by all subjects once daily in their UPDD, on a scale of 0 (none) to 3 (severe) (see Table 2). A weekly ISS score (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. Partially missing diary entries will be handled in the same way described for the hives severity score.

A complete itch response is defined as ISS7 = 0.

Table 2 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)

2.2 Secondary Objectives and Endpoints

The secondary objectives of the study are to further characterize the efficacy and safety of lirentelimab SC in adult subjects with CSU as measured by the following:

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

2.3 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:

- Impact on subject's [redacted] based on change from baseline in [redacted] at Week 12
- 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]

2.3.1 [redacted]

The [redacted] is a [redacted] questionnaire for assessing [redacted] and will be administered to the subject when in the clinic. Each item is rated on a scale of [redacted] and a total score is calculated (range, [redacted]). Higher scores indicate [redacted].

2.3.2 [redacted]

The [redacted] is a [redacted] questionnaire used to measure the [redacted] of an affected person over the past week. The format is a simple response [redacted]

[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. The scoring of each question is defined in Table 3.

Table 3 [redacted] Scoring

Response Per Question	Score
[redacted]	

The [redacted] is calculated by summing the score of each question resulting in a maximum of [redacted] and a minimum of [redacted] The higher the score, the more [redacted] (Table 4).

Table 4 Meaning of [redacted] Scores

Score	Definition
[redacted]	

The [redacted] can be analyzed under six headings as shown in Table 5.

Table 5 Detailed Analysis of [redacted]

Heading	Question Number(s)	Score Maximum
[redacted]		

Heading	Question Number(s)	Score Maximum
[redacted]		

Interpretation of incorrectly completed [redacted] questionnaires:

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

2.3.3 [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]. 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] points.

2.4 Safety Objectives and Endpoints

The safety objective of the study is to evaluate the study drug safety profile using the following safety endpoints:

- Treatment emergent adverse events (TEAE) including severity, relationship to study treatment, serious adverse events (SAE), and adverse events (AE) leading to study drug withdrawal
- Anti-drug (lirentelimab) antibody (ADA)
- Changes in Laboratory tests
- Changes in Physical examination
- Changes in vital signs

3. Study Design

3.1 General Description

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 during 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 goal can be achieved with fewer sites and 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 H1-AH prior to screening will undergo a 2-week eligibility screening period. Subjects who are not on a stable approved 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 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 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 open-label extension (OLE) period of the study to receive 6 doses of lirentelimab SC, 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.

The overall schedule of procedures and assessments is presented in Table 6.

Table 6 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	**Day 8** (±3)	**Day 15** (±5)	**Day 29** (±5)	**Day 43** (±5)	**Day 57** (±5)	**Day 71** (±5)	**Day 85** (±5)	**Day 127** (±5)	**Day 155** (±5)
				Dose 1		**Dose 2**	**Dose 3**	**Dose 4**	**Dose 5**	**Dose 6**			
	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]
FSH: Follicle-Stimulating Hormone
FUP: Follow-up
hCG: Human Chorionic Gonadotropin
IRT: Interactive Response Technology
UAS7: Weekly Urticaria Activity Score
[redacted]

EOS: End of Study IP: Investigational Product UPDD: Urticaria Patient Daily Diary

Table 6 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 of the protocol).

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 Score (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] will 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).

Table 6 Notes cont.

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 of the study protocol.

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 of the study protocol.

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.

3.2 Methods of Assigning Subjects to Treatment Groups

Approximately 130 subjects (65 per arm) will be randomized to treatment with lirentelimab SC or placebo SC in a 1:1 ratio. Stratified permuted block randomization will be used. Randomization will be stratified based on UAS7 score (16–27 vs. 28–42) and on Omalizumab experience for the treatment of CSU (omalizumab-exposed vs. omalizumab-naïve). An Interactive Response Technology System (IRT) will be used to perform the randomization.

3.3 Treatment Blinding

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

3.4 Determination of Sample Size

A sample size of 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.

4. Definitions

4.1 Terminology and Definitions

Table 7 Terminology and Definitions

Terminology	Definition
Baseline	Baseline for non-daily assessment (e.g., laboratory tests) is defined as the non-missing value collected most recently to and before the time of the very first dose of study drug. Baseline Patient Reported Outcome (PRO) data will be the average or the sum of the weekly PRO data collected in the last 7 days prior to Day 1 depending on the outcome under consideration.
Concomitant Medications and Procedures	Medications and procedures with a stop date before the treatment dosing date will be considered prior medications/procedures. Medications and procedures with a start or stop date on or after the treatment dosing date will be considered concomitant. All medications/procedures marked as ongoing are concomitant.
Study Day	Study Day 1 is defined as the date on which a subject received the first dose of study drug. For visits prior to the first dose of study drug, Study Day is calculated as Visit Date – Day 1 Date. For visits after the first dose, Study Day is calculated as Visit Date – Day 1 Date +1.
Study Week	Study Week for PRO analysis is defined as 7 days a week starting from the day of first dose (Day 1). Details are provided in Section 5.2.

4.2 Target of Estimation

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?"

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

4.2.1 Population Targeted by the Scientific Question

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

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

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

4.2.3 Treatment

Lirentelimab SC or placebo SC administered to subjects on Days 1, 15, 29, 43, 57, and 71 for a total of 6 doses.

4.2.4 Intercurrent Events

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

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

4.2.5 Strategy for Handling Intercurrent Events

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

During the double-blind portion of the study, use of the following prohibited medications for reasons unrelated to CSU or rescue medications for the purposes of alleviating symptoms of CSU (see Appendix 1) will be deemed an ICE and efficacy data for the affected subject will be handled as follows:

- Antihistamines – Use of any new H1-AH or additional doses of an H1-AH above the stable baseline dose are prohibited. Subject-entered data for the day after the prohibited medication was used will be set to missing and this will apply for each day of prohibited medication use.
- Systemic corticosteroids – Use of systemic corticosteroids at any dose and for a duration of less than 3 consecutive days will result in the subject's efficacy data for a period of 7 calendar days will be set to missing beginning with the first day of systemic corticosteroid use and extending to a 7 day period following the last dose. Use of systemic corticosteroids for 3 or more days will result in censoring of all efficacy data from the first day of corticosteroid treatment, i.e., this

censoring rule is equivalent to using all the data up to first day of corticosteroid treatment. An appropriate method for handling missing data through statistical modeling (e.g., multiple imputation [MI]) will be used for continuous endpoints. For binary endpoints, efficacy outcome will be set to non-responder status.

- Immunosuppressants, Immunomodulators and Biologics – Use of any immunomodulator, immunosuppressant or biologic will result in the premature withdrawal of the subject from the study and the censoring of all efficacy from the initiation of that therapy, i.e., this censoring rule is equivalent to using all the data up to first day of the prohibited therapy. An appropriate method for handling missing data through statistical modeling (e.g., multiple imputation [MI]) will be used for continuous endpoints. For binary endpoints, efficacy outcome will be set to non-responder status.

Blinded adjudication of prohibited medication uses for rescue or for reasons unrelated to symptoms of CSU will be implemented before database lock.

4.2.6 Summary Measure of the Estimand

Least squares mean (LSM) (and standard error [SE]) of change from baseline in UAS7 to Week 12 and the between treatment difference in the lirentelimab SC and placebo SC groups LSM.

5. Statistical Methods

5.1 General Methodology

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

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

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

addition, for summary of disposition and subject baseline characteristics, the presentation will include both treatment groups combined.

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

- Sample size (n, N) and number of missing responses (if displayed): Integer
- Mean, confidence interval, and median: Same number of decimal places as reported/collected
- Standard deviation: Same number of decimal places as reported/collected
- Percentiles, minimum, maximum: Same number of decimal places as reported/collected
- Odds Ratio: 2 decimal places
- Percentage: 1 decimal place generally, or 2 decimal places for <0.1%, or no decimal places for 0% and ≥100%
- P-value: 4 decimal places
- WBC: 2 decimal places as 0.01×10^9/L
- Height/Weight/BMI: 1 decimal place

The data summaries will be accompanied by individual subject data listings. All data available from questionnaires, eCRF, and external transfer (labs) will be listed and will include relevant subject information, e.g., treatment group and study day. The listings will be sorted in the order of treatment group, subject ID, assessment name and date/time.

Dates will be presented in the ISO-8601 format YYYY-MM-DD. Times will be displayed in 24-hour clock format. Numbering for tables, figures and listings will follow ICH E3 Guideline (ICH, 1996).

Alternative methods of analysis of the data may be considered prior to database lock, and reason for departure from the planned methods will be documented in an amendment to the SAP or in the CSR.

5.2 Visit Window and Unscheduled Assessments

Data collected for study assessments provide information on the status of the subject at a given time point. For all the non-daily, by-visit assessments, no analysis window will be defined. The by-visit summaries will be performed based on their associated visits.

In the event of multiple values from unscheduled or early termination assessments associated with a single visit, the value closest to the scheduled visit target study day will be used for analyses. If 2 values tie as closest to the time point (for example, 1 value is before and the other value is after the

time point), then the later value will be selected. Data collected at all visits will be included in the data listings with visit presented as reported by the site.

Post-baseline weekly diary endpoints will be derived from subject daily diary windows anchored on day of first dose (Study Day 1) and day of last dose. Weeks 1 through 9 are defined in Table 8.

Table 8 Analysis Week Definitions Based on Scheduled Visits

Analysis Week	Study Days
1	1 – 7
2	8 – 14
3	15 – 21
4	22 – 28
5	29 – 35
6	36 – 42
7	43 – 49
8	50 – 56
9	57 - 63

The diary window of Week 12 is the 7 days prior to the earlier of a) 14 days after Day 71 dose; or b) Open Label Extension Day 1 dose. In the case of diary non-compliance (fewer than 4 completed daily diaries in the Week 12 diary window), the start of the window can be extended back one day at a time until 4 completed daily diaries are obtained, or up to the day of Day 71 dose, whichever is reached first. If the Week 12 diary window still has fewer than 4 daily diaries after extending the start of Week 12 diary window to the day of Day 71 dose, the Week 12 diary window is defined as 7 days and the value of the window is set to missing.

The Week 11 diary window begins on the day of Day 71 dose and ends on the earlier of a) six days after Day 71 dose; or b) 1 day prior to the start of the Week 12 diary window.

The diary window of Week 10 begins on the latter of a) 7 days prior to Day 71 dose; or b) Study Day 64 and ends on the day before Day 71 dose.

If after constructing the diary windows there are fewer than 4 completed daily diaries for any week, the value of that week is set to missing and subject to imputation rules.

5.3 Adjustment for Covariates

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

5.4 Data Handling Conventions

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

Adverse events with incomplete start or stop dates (i.e., either day or month is missing) will be considered treatment-emergent adverse events (TEAE) unless the partial start date or the stop date confirms the AE started or ended prior to Study Day 1 (e.g., the day of the AE start date is unknown but the month and year indicate that the AE starts prior to Study Day 1). Adverse events with missing relationship to study drug will be included in the "Related" category for the summary tables and footnoted. Adverse events with missing severity will not be included in the by-severity summary table but will be footnoted in the table.

When there is incomplete information regarding dosing dates for prior and concomitant medication, the medication will be considered as a concomitant medication unless it contradicts with the stop date. For example, a medication will be considered a prior medication if the month and year of the end date indicates a date before Study Day 1 even though the start date could be missing.

5.5 Independent Safety Monitoring Committee

An independent Data Monitoring Committee (iDMC) has been convened for this study for purposes of safety monitoring. The iDMC will meet at established intervals (as per the iDMC charter) throughout the study and will also convene as necessitated by data and/or safety reviews. The iDMC will not be tasked with any efficacy analyses.

5.6 Timing of Data Analyses

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

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

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

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

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

5.7 Interim Analysis

No interim analysis will be conducted for this study.

5.8 Multicenter Study

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

5.9 Multiple Comparisons/Multiplicity Adjustment

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

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

- If $p \leq 0.05$ for primary endpoint, then reject the null hypothesis that lirentelimab SC is no different from placebo SC and accept the alternative hypothesis that lirentelimab SC is superior to placebo SC in improving UAS7 score.
- If $p \leq 0.05$ for primary endpoint, the hypothesis tests for the secondary endpoints will proceed in the prespecified order (see Section 2.2). If at any point during the analysis of the secondary endpoints, the statistical test is not significant at 2-sided α=0.05 level, the hypothesis testing procedure will stop. Lirentelimab SC will be deemed superior to placebo SC for all endpoints prior to the stop.

5.10 Examination of Subgroups

Key endpoints will be summarized by subgroup to assess the consistency of the treatment effect across each of these subgroups. For any subgroup, if there are zero subjects within a stratification

stratum in any treatment group, the statistical model will not be adjusted by the stratification factors. Subgroups to be considered are:

- Sex (Male, Female)
- Age group (<65, ≥65)
- Race (White, Non-White)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Region (U.S., non-U.S.)
- Baseline weekly itch severity score (<13, ≥13)
- History of angioedema at screening (Yes, No)
- Prior omalizumab experience for the treatment of CSU (exposed, naïve)
- Baseline UAS7 score (16–27, 28–42)
- Duration of disease prior to baseline (<2, 2-10, >10 years)
- Screening IgE (≥43 kU/L, <43 kU/L)

6. Statistical Analysis

6.1 Analysis Populations

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

6.1.1 Safety Population

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

6.1.2 Intent-to-Treat Population

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

6.1.3 Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population will be defined as all randomized subjects who received at least one dose of study drug and had no major protocol violations based on key inclusion and exclusion criteria defining the population of interest (i.e., defined as not meeting inclusion criteria number 3, 4, 5, or 6).

The per protocol (PP) population will include the subjects in the mITT population who do not have

any major protocol deviations or violations and have received all 6 doses of study medication (see Section 6.3 for list of protocol deviations and violations).

6.2 Disposition of Subjects

Subject demographics and reasons for screening failure will be summarized for screen-failed subjects. Subjects (n and %) who completed or discontinued from the study will be tabulated by treatment group and for both treatment groups combined. The primary reasons for study discontinuation will be included in the tabulation. The primary reasons may include, but are not limited to, any of the following:

- Subject withdrew consent
- Lost to follow-up
- Administrative reason
- Adverse event
- Investigator decision
- Failure to follow required study procedures
- Other

Subject disposition will be summarized for the ITT population. Subject counts for the Safety, mITT, and PP populations will be included in the table. A data listing for subject disposition will be presented for the ITT population.

6.3 Protocol Deviations and Violations

Protocol deviations will include, but are not limited to

- Non-compliance with scheduled study visit
- Non-compliance with study treatment
- Received prohibited medications (see Protocol Section 9.1)
- Any major violations of efficacy-related entry inclusion or exclusion criteria (defined as not meeting inclusion criteria number 3, 4, 5, or 6)
- Non-compliance with study assessment procedures

Subjects with major protocol deviations will be listed. The listing will include a brief description of the deviation, deviation category, and if applicable, study day when deviation occurred along with other pertinent information. If warranted by the sample size, subjects (n and %) with major protocol

deviations will be tabulated by treatment group and by deviation category.

Subjects who are excluded from the PP population will be listed with reasons for exclusion.

6.4 Demographics and Baseline Disease Characteristics

The demographic and baseline characteristics variables are described in Section 5.10.

Descriptive statistics for these variables will be presented for all populations, by treatment group, and both treatment groups combined. Continuous variables will be summarized with n, mean, SD, and median. Categorical variables will be summarized with n and % of subjects for each category for the mITT, and PP populations.

6.5 Medical History

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

6.6 Electrocardiogram

A listing of electrocardiogram (ECG) overall interpretations at screening visit will be provided.

6.7 Pregnancy Test

A listing of pregnancy test results will be provided.

6.8 Treatments

6.8.1 Treatment Compliance

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

The compliance with study treatment will be calculated as follows:

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

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

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

6.8.2 Prior, Concomitant, and Newly Initiated Medications

Prior medications and concomitant medications will be extracted from the Prior/Concomitant Medication CRF. Medications taken prior to Study Day 1 will be considered as prior medications, medications taken on or after Study Day 1 will be considered as concomitant medications, and newly initiated medication refers to any medication with a start date ≥ Study Day 1. Note that a Prior Medication may also be a Concomitant Medication if the start date is prior to Study Day 1 and the end date is on/after Study Day 1. Medications will be coded using the WHO Drug Dictionary (WHODRUG GLOBAL September 2022 release) for preferred term (PT) and Anatomical Therapeutic Chemical (ATC) classification.

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

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

6.9 Analyses of Efficacy Endpoints

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

H_0: No treatment difference between lirentelimab SC and placebo SC

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

Omalizumab experience for the treatment of CSU (exposed, naïve) and UAS7 score (16–27, 28–42) will be the 2 stratification factors for subject randomization and will be accounted for in the statistical modeling for efficacy. In addition, if it is evident that the primary endpoint is confounded by baseline disease characteristics at study entry, then the primary efficacy analysis will be adjusted for the effects of these variables.

6.9.1 Analysis of Primary Efficacy Endpoint

The primary endpoint will be analyzed using analysis of covariance (ANCOVA) using the imputed data set described below. The synthesizing method will be used to combine the results from multiple imputations. The least square (LS) mean, standard error (SE), and 95% confidence interval (CI) for each treatment group and for the between group difference will be derived from the ANCOVA model

with treatment as factor, and baseline UAS7 score and omalizumab experience for the treatment of CSU (exposed, naïve) as covariates. The hypothesis test for the treatment effect will be carried out by the F-test.

For the analysis described above, missing data from subjects who prematurely discontinue the randomized treatment, initiate any treatment adjustments as outlined in Section 4.2.5 (e.g., use of prohibited or rescue medication), or missing daily PRO scores as described in Section 2.1 will be imputed using multiple imputation (MI) techniques. There are five steps in the MI process.

1) Check missing data patterns.
2) Impute non-monotonic or intermittent data until only monotone missing data remains.
3) Use monotone regression to impute monotone missing data and create multiply imputed data sets.
4) Run the primary efficacy analysis (ANCOVA using SAS PROC MIXED) on the multiply imputed data sets.
5) Use SAS PROC MIANALYZE to combine the efficacy output to get a single estimate from all the imputed data sets.

6.9.1.1 Step 1. Checking missing data patterns

For this study, the missing data patterns will be checked by treatment and visits (baseline to Week 12). There are 3 steps to this process:

Create dataset for efficacy measure including visits from baseline to Week 12

```
data mi_chk1; set datax;
where paramcd="UAS7" and baseline <= visit <=Week 12;
run;
```

Transpose dataset to display each visit as one column:

```
proc sort data = mi_chk1; by treatment  id;
proc transpose data=mi_chk1 out=mi_chk2 prefix='';
by treatment   id;
id avisitn;
var aval;
run;
```

Use PROC MI with the NIMPUTE=0 option to create the "Missing Data Patterns" table for the specified variables:

```
ods output MissPattern=missp;
proc mi data=mi_chk2 NIMPUTE=0;
```

```
  by treatment;
  var visit0(i.e., baseline) – visit12 (i.e., Week 12);
run;
```

6.9.1.2 Step 2. Impute non-monotonic/intermittent data until only monotone missing data remains.

Fill in the intermittent missing data using the following code.

```
proc sort data = mi_chk2; by treatment;
proc mi data=mi_chk2 seed=12345 NIMPUTE=50 out=MI;
  by treatment;
  mcmc impute=monotone;
  var Visit0 – Visit12;
  run;
```

6.9.1.3 Step 3. Use monotone regression to impute monotone missing data and create multiply imputed data sets.

```
proc sort data = mi; by _Imputation_;
proc mi data=mi out=mi_reg seed=54321 nimpute=1;
by _Imputation_;
var treatment Visit0 – Visit12;
class treatment;
monotone regression;
run;
```

6.9.1.4 Step 4. Run the efficacy analyses (PROC MIXED) on the multiply imputed data sets.

```
/** Recalculate change from baseline at Week 12**/
data UAS7_imputed;
  set mi_reg;
  chg=Visit12 – Visit0;
run;

proc sort data=UAS7_imputed out=UAS7_imputed1;
  by _imputation_;
run;

/** ANCOVA by imputation **/
ods output diffs=diffs lsmeans=lsm;
proc mixed data=UAS7_imputed1 method=reml;
  by _imputation_;
  class region omalizumab experience TREATMENT;
  model CHG= region omalizumab experience Visit0 TREATTMENT;
  lsmeans TREATMENT / diff;
quit;
```

```
ods output close;
```

6.9.1.5 Step 5. Combine estimates of the 50 PROC MIXED models to create an overall estimate and a relative efficacy score.

```
/** Combine LS Means (by treatment and difference) **/
data lsmdiff;
  set lsm diffs(in=d);
  if d then treattment='DIFF';
run;
proc sort;by TREATMENT;run;

/** Synthesized results **/
ods output ParameterEstimates=SYNDIF;
proc mianalyze data=LSMDIFF alpha=0.05;
   by TREATMENT;
   modeleffects ESTIMATE;
   stderr stderr;
run ;
ods output close;
```

The primary efficacy analysis will be performed on the mITT population. The PP population will be analysed as a supporting analysis.

6.9.2 Analysis of Secondary and Exploratory Efficacy Endpoints

The binary secondary and exploratory efficacy endpoints will be analyzed using the Cochran-Mantel-Haenszel test adjusted by omalizumab experience for the treatment of CSU (exposed, naïve), UAS7 score (16–27, 28–42), and region (U.S., non-U.S.) at Week 12. A sample SAS code is as follows:

```
* COMPUTES CMH P-VALUE AND NEWCOMBE COMMON RISK DIFFERENCE ;
ods output CMH=PVAL(where=(althypothesis='Row Mean Scores Differ'))
CommonPdiff=DIFF;
proc freq data=ADEF ;
      tables UAS7*OMALIZUMAB_EXPERIENCE*REGION*TRTP*RESP / cmh(MF)
commonriskdiff
(cl=NEWCOMBE) ;
run ;
```

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

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

```
* COMPUTE 95% EXACT CONFIDENCE INTERVAL FOR %RESPONSE FOR INDIVIDUAL
TREATMENT ;
ods output BinomialCLs=CL ;
proc freq data=ADEF ;
      table RESP / out=CNTS bin(cl=midp) ;
      by TRTP ;
run;
* COMPUTE 95% EXACT CONFIDENCE INTERVAL AND FISHERS EXACT P-VALUE FOR
BETWEEN TREATMENT DIFFERENCE ;
ods output FishersExact=PVAL(where=(name1='XP2_FISH'))
RiskDiffCol2=DIFF(where=(row='Difference') ;
proc freq data=ADEF ;
      table TRTP*RESP / riskdiff(cl=exact) exact  ;
run ;
```

For the analysis described above, missing data from subjects who prematurely discontinue the randomized treatment, initiate any treatment adjustments as outlined in Section 4.2.5 (e.g., use of prohibited or rescue medication), or missing daily PRO scores as described in Section 2.1 will be imputed using non-response imputation.

To assess the impact of the above "non-responder" rule, the missing data strategy will employ mixed model for repeated measures (MMRM) technique. This approach assumes missing observations are missing at random and borrows information from subjects in the same treatment group considering the missingness of data through the correlation of the repeated measurements. The SAS procedure PROC GLIMMIX will be used for this purpose. The model will include treatment, region, omalizumab experience for the treatment of CSU (exposed, naïve), UAS7 score (16–27, 28–42), visit, and treatment-by-visit-interaction as fixed categorical effects, and baseline and baseline-by-visit-interaction as fixed continuous effects. The model will provide odds ratio, standard error, two-sided 95% confidence interval for odds ratio and p-values at time points of interest.

All secondary and exploratory efficacy endpoints of continuous nature will utilize MMRM procedure after applying the primary censoring rule, i.e., the rule will censor data after permanent study drug discontinuation or after rescue therapy that applies the censoring rule as described in Section 4.2.5. This censoring rule is equivalent to using all the data up to discontinuation or rescue.

The MMRM model will include fixed effects for baseline value, omalizumab experience for the treatment of CSU (exposed, naïve), UAS7 score (16–27, 28–42), country, treatment, study week, the treatment-by-week interaction, and the baseline-by-week interaction and allow for random subject effects. Treatment and week will each be fitted as categorical variables. The model will assume unstructured covariance structure. If the model with unstructured covariance does not converge, then other covariance structures will be considered to model the within-subject errors. The Kenward-

Rogers approach for computing denominator degrees of freedom will be used to account appropriately for pooling of within-subject and between-subject variance estimates. The LS and 95% CI for the difference between groups will be estimated using the simple contrast at each time point. Below is an example of the SAS code for the MMRM:

```
proc mixed data=CONTINUOS method=reml;
  class TREATMENT USUBJID AVISITN REGION USA7_SCORE (16–27, 28–42)
OMALIZUMAB_EXPERIENCE;
  model CHANGE= BASELINE_OF_OUTCOME USA7_SCORE (16–27, 28–42)
OMALIZUMAB_EXPERIENCE TREATMENT AVISITN REGION
TREATMENT*AVISITN BASELINE_OF_OUTCOME *AVISITN / DDFM=KR;
REPEATED AVISITN / SUBJECT=USUBJID (TREATMENT) TYPE=UN;
RANDOM REGION;
LSMEANS TREATMENT*AVISITN / PDIFF CL;
RUN;
```

Where TREATMENT = planned treatment group in numeric (1 = placebo SC, 2 = lirentelimab SC); AVISITN = time point in Weeks.

6.10 Analysis of Pharmacokinetic Endpoint

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

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

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

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

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

6.11 Safety Analyses

6.11.1 Adverse Events

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

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

The following AE incidence tables will be presented.

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

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

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

6.11.2 Laboratory Test

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

Shift tables will be presented, in which, lab test results at baseline and post-baseline visit will be classified into below (<LLN), within (≥LLN and ≤ULN), and above (>ULN) normal ranges. Subject incidences (n and %) will be presented for the shift from baseline to the post-baseline visits.

Note that the analysis window will be applied for the visits.

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

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

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

6.11.4 Electrocardiogram

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

6.11.5 Physical Examination

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

6.11.6 Analysis of Anti-Drug Antibodies

A data listing of anti-drug-antibodies (ADA) results will be provided for all subjects. Number (%) of subjects who are confirmed ADA-positive at any time after receiving study drug and number (%) of

subjects who are confirmed ADA-positive at the end of study will be cross-tabulated by their ADA status and titers at predose.

7. Validation

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

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

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

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

8. References

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

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

9. Appendices

9.1 Appendix 1: Intercurrent Events and Listing of Prohibited Medication/Treatments and Potential Rescue Medications for CSU

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

9.1 Appendix 1: Intercurrent Events and Listing of Prohibited Medication/Treatments and Potential Rescue Medications for CSU

Prohibited medications are defined as therapies that should not be taken during the course of the study either because of a potential impact on the assessment of efficacy and/or subject safety. Rescue medications/treatments are defined as any therapy or treatment taken during the course of the study for the specific purpose of alleviating CSU symptoms that may have an impact on the assessment of efficacy and includes: systemic medications such as systemic corticosteroids, increased daily dose or addition of a new H1-AHs, immunosuppressants, immunomodulatory medications, and biologics. Detailed definitions of ICE and data handling strategy for ICE are described in section 4.2.5.

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

1) The use or initiation of any new H1-AH or increase in the total daily dose, as compared to baseline, of an H1-AH for the purpose of treating CSU at any point in the study will be considered rescue therapy H1-AH: ATC code is R06A

2) The use or initiation of topical corticosteroids for the purpose of treating skin conditions other than CSU at any point in the study will be not be considered rescue therapy but should be avoided if possible. If unavoidable, lower potency topical steroids over the least surface area possible and for the shortest duration should be utilized: ATC code is D07A
   High Potency TCS: ATC codes D07AC or D07AD
   Low or moderate potency TCS: ATC code D07, excluding D07AC or D07AD

3) Prohibited systemic medications (including systemic corticosteroids, H2-AH, immunosuppressants, immunomodulators, hydroxychloroquine, oral doxepin, IV immunoglobulins, and biologics)

   Systemic corticosteroids: ATC code is H02
   H2-AHs: ATC code is A02BA
   Immunosuppressants or immunomodulators: ATC code is L04
   Mycophenolate: ATC code is L04AA06
   Methotrexate: ATC code is L04AX
   Interferons: gamma: ATC code is L03AB where Preferred Terms include interferon gamma, interferonalfa-2b
   Leukotriene inhibitors: ATC code is R03DC where Preferred Term includes Ibudilast, Montelukast, Pranlukast, and Zafirlukast
   Oral calcineurin inhibitors: ATC code is L04AD where Preferred Term includes Ciclosporin, Cyclosporin, Tacforius, Tacrolimus, Voclosporin
   Hydroxychloroquine: ATC code is P01BA02
   Oral doxepin: ATC code is N06AA12
   IV immunoglobulins: ATC code is J06B

Janus Kinase inhibitors (JAKi): ATC code is L01EJ where Preferred Term includes Delgocitinib, Fedratinib, Pacritinib, Ruxolitinib and ATC code is D11AH with Preferred Term Abrocitinib
TNF inhibitors: ATC code is L04AB where Preferred Term includes Adalimumab, Afelimomab, Certolizumab, Etanercept, Golimumab, Infliximab, Opinercept, Ozoralizumab

Biologics:
Agents For CSU, Excluding Corticosteroids: ATC code is D11A where preferred terms include Dupilumab, Tralokinumab
CD20 inhibitors: ATC code is L01F where preferred terms include Obinutuzumab, Ofatumumab
Selective Immunosuppressants: ATC code is L04AA where preferred terms include Abatacept, Abetimus, Alemtuzumab, Anifrolumab, Apremilast, Baricitinib, Begelomab, Belatacept, Belimumab, Belumosudil, Deucravacitinib, Eculizumab, Efalizumab, Emapalumab, Filgotinib, Fingolimod, Inebilizumab, Itacitinib, Natalizumab, Ocrelizumab, Ofatumumab, Ozanimod, Peficitinib, Pegcetacoplan, Ponesimod, Ravulizumab, Sutimlimab, Teprotumumab, Teriflunomide, Tofacitinib, Upadacitinib, Vedolizumab
Interleukin Inhibitors: ATC code is L04AC where preferred terms include Anakinra, Basiliximab, Bimekizumab, Briakinumab, Brodalumab, Canakinumab, Daclizumab, Guselkumab, Ixekizumab, Netakimab, Olokizumab, Rilonacept, Risankizumab, Sarilumab, Satralizumab, Secukinumab, Siltuximab, Sirukumab, Spesolimab, Tildrakizumab, Tocilizumab, Ustekinumab
Unspecified Immunosuppressants: No ATC code with Preferred Term including Barzolvolimab, Fezakinumab, Fletikumab, Gevokizumab, Gusacitinib, Ladarixin, Lebrikizumab, Ligelizumab, Mirikizumab, Nemolizumab, Olamkicept, Tabalumab, Tregalizumab
Biologics for Airway Disease and other indications: ATC code R03D with Preferred Term including Benralizumab, Mepolizumab, Omalizumab, Reslizumab, Roflumilast, Tezepelumab and ATC code is R03DX with Preferred Term including Rituximab

Other potential treatments for CSU:
The use of plasmapheresis, ultraviolet A or B (UVA or UVB), psoralen + UVA (PUVA), other phototherapy is not permitted during the study. The use of a tanning bed will not be considered rescue therapy or an ICE.

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