An Open-Label, Pilot Study to Assess the Efficacy and Safety of AK002 (Siglec-8) in Subjects with Antihistamine-Resistant Chronic Urticaria

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Statistical Analysis Plan

Protocol Title	An Open-Label, Pilot Study to Assess the Efficacy and Safety of AK002 (Siglec-8) in Subjects with Antihistamine-Resistant Chronic Urticaria
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List of Abbreviations

AE	Adverse event
[redacted]	[redacted]
AH	Antihistamine
ATC	Anatomical-Therapeutic-Chemical
CholU	Cholinergic Urticaria
[redacted]	[redacted]
[redacted]	[redacted]
CI	Confidence Interval
CMR	Clinically Meaningful Response
CR	Complete response
CRF	Case Report Form
CSR	Clinical study report
CSU	Chronic Spontaneous Urticaria
CSU-XN	Chronic Spontaneous Urticaria – Xolair Naïve
CSU-XF	Chronic Spontaneous Urticaria – Xolair Failure
CU	Chronic Urticaria
[redacted]	[redacted]
DC	Disease Control
[redacted]	[redacted]
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FSH	Follicle-Stimulating Hormone
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IgE	Immunoglobulin E
IRB	Institutional Review Board
IV	Intravenous (ly)
MedDRA	Medical Dictionary for Regulatory Activities
MCIR	Minimally Clinically Important Response
MCID	Minimally Clinically Important Difference
PK	Pharmacokinetics
PP	Per-Protocol population
PR	Partial response
PT	Preferred term
p-value	Probability value
QoL	Quality of Life

SAE	Serious adverse event
SD	Standard deviation
[redacted]	[redacted]
SAP	Statistical Analysis Plan
SOC	System organ class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
UAS	Urticaria Activity Score
UAS7	Weekly Urticaria Activity Score
UCT	Urticaria Control Test
UF	Urticaria Factitia
UPDD	Urticaria Patient Daily Diary
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

Revision History

Version Date	Version Number	Description
31 Aug 2018	1	First version of the Statistical Analysis Plan
13 Feb 2019	1.1	Add clarifications and incorporate changes needed per the protocol amendments

1. Introduction

This statistical analysis plan (SAP) describes the rules and conventions to be used in the analysis and presentation of efficacy and safety data as planned for the clinical protocol. It describes, in detail, the data and variables to be summarized or analyzed, including specifications of the analytical methods to be performed. The statistical analysis plan presented in this document will supersede the statistical analysis methods described in the clinical protocol. 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). This SAP is based on the clinical study protocol AK002-006, Amendment 4/4.1, dated 11 Jan 2019 and its associated electronic case report forms (eCRF).

2. Study Objectives

2.1 Primary Objective

The primary objective is to assess the efficacy and safety of AK002 in subjects with Chronic Urticaria (CU). Efficacy will be assessed by the urticaria control test [UCT] score.

2.2 Secondary Objectives

The secondary objectives of the study are to assess other measures of efficacy and pharmacodynamics of AK002.

3. Study Design

3.1 General Description

This is an open-label, pilot study to assess the efficacy and safety of AK002 in subjects with antihistamine-resistant chronic urticaria. The study comprises a screening period of 4 weeks, with daily oral intake of standard-dose (once daily) second-generation antihistamine (AH) (standard of care, with on-demand intake of up to 3 additional AH tablets per day). The treatment period comprises a daily oral intake of standard-dose second-generation AH and AK002 administered by IV infusion at Days 1, 29, 57, 85, 113, and 141. The primary and secondary endpoints will be evaluated at Week 10, 2 weeks after last dose, for subjects enrolled under Protocol Amendment 2.1 and Week 22, 2 weeks after last dose, for all remaining subjects (i.e., those on study during Protocol Amendment 3), and then patients will be followed for an additional 4 weeks (Week 24). The study design is presented schematically in Table 1.

Table 1 Schedule of Assessments for the Main Study

Description	Visit 1	Visit 2	Visit 3	Visit 4	Visits 5, 6, 7	Visit 8	Visit 9	Visit 10
	Day -28	Day 1	Day 29 (± 2)	Day 57 (± 2)	Days 85, 113, and 141 (± 2)	Day 155 (± 2)	Day 169 (± 2)	Day 197 (± 2)
	Week -4	Week 0	Week 4	Week 8	Weeks 12, 16, and 20	Week 22	Week 24	Week 28
	Screening	Baseline/Dosing	Dosing	Dosing	Dosing[r]	Response Assessment[t]	Response Assessment	End of Study/ Early Term.
Informed consent	x[a]							
Eligibility assessment/ confirmation	x	x[b]						
Demographic data	x							
Medical history	x							
Prior CU treatment	x							
Prior/concomitant medication	x	x	x	x	x	x	x	x
Rescue medication use		x	x	x	x	x	x	x
Study Drug administration[c]		x	x	x	x			
Patient diary[d,s]	x	x	x	x	x	x	x	x
UAS7 [redacted]		x	x	x	x	x	x	x
[redacted]		x	x	x	x	x	x	x
[redacted]		x	x	x	x	x	x	x
UCT		x	x	x	x	x	x	x
[redacted][q]	x	x	x	x	x	x	x	x
[redacted]		x	x	x	x	x	x	x
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] and FricTest®)[e]	x (if applicable)	x (if applicable)	x (if applicable)	x (if applicable)	x (if applicable)	x (if applicable)	x (if applicable)	x (if applicable)
Skin biopsy[p]		x				x		

Table 1 Scheduled of Assessments (continued)

Description	Visit 1 Day -28 Week -4 Screening	Visit 2 Day 1 Week 0 Baseline/Dosing	Visit 3 Day 29 (± 2) Week 4 Dosing	Visit 4 Day 57 (± 2) Week 8 Dosing	Visits 5, 6, 7 Days 85, 113, and 141 (± 2) Weeks 12, 16, and 20 Dosing[r]	Visit 8 Day 155 (± 2) Week 22 Response Assessment[t]	Visit 9 Day 169 (± 2) Week 24 Response Assessment	Visit 10 Day 197 (± 2) Week 28 End of Study/ Early Term.
Anti-drug antibodies[f]		x	x		x	x		x
PK analysis[f]		x	x		x	x		x
Blood safety[g]	x	x	x	x	x	x	x	x
Blood biomarkers[o]		x	x	x	x	x	x	x
Serology[h]	x							
Urinalysis	x[i]	x	x	x	x	x	x	x
Urine pregnancy		x	x	x	x	x	x	x
Serum pregnancy[j]	x							
Stool for ova and parasite	x							
Physical examination[s]	x[k]	x[l]	x[l]	x[l]	x[l]	x[l]	x[l]	x[l]
Vital signs[m]	x	x	x	x	x	x	x	x
Weight	x	x	x	x	x	x	x	x
12-lead ECG[n]	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x

Table 3 Notes

a) Subjects who do not meet all eligibility criteria at Screening, or who qualify at Screening but are not enrolled, may be assigned a new Patient ID number and re-screened once. Subjects re-screened within 30 days of signing the initial consent will not need to sign a new ICF providing there have been no changes to the ICF.

b) Baseline is defined as up to 48 hours prior to first dose.

c) AK002 will be administered as a single peripheral IV infusion. Please refer to the Pharmacy Manual for detailed instructions on preparations, administration, and infusion rate.

d) Subjects should complete the [redacted] on a weekly basis. On weeks where a clinic visit is not scheduled, the [redacted] should be completed at home.

Table 3 Notes (continued)

e) Subjects will be administered only the instruments that are relevant to their condition (see **Error! Reference source not found.**). FricTest will be assessed, if relevant, at every visit. The PCE can be performed at Visit 1 for diagnostic reasons and will be assessed at Visits 2 (at least 24 hours prior to dose), 8, and 10 only.

f) ADA will be obtained Visits 2, 3, 5, 8 and 10. An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected. PK will be analyzed retroactively using backup blood samples.

g) Hematology, Chemistry and CBC with differential.

h) Serology at Screening includes hepatitis B surface antigen (HBsAG), hepatitis C antibody, hepatitis B core antibody (anti-HBc), and human immunodeficiency virus (HIV).

i) At Screening, include urine drug screening (alcohol, amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine, methadone, methaqualone, opiates, phencyclidine) and urine cotinine tests.

j) Blood for serum pregnancy tests at Screening Visit; blood for FSH is to be obtained only to confirm post-menopausal status.

k) A complete PE will be performed by either the Investigator or designee as noted in Section **Error! Reference source not found.**.

l) A symptom-directed PE, including assessments of possible infusion site reactions, will be performed by the Investigator or designee as needed.

m) Vital signs, including supine systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate, will be taken after the patient has been in the supine position for ≥5 minutes and before any blood draw. On AK002 dosing days, vital signs will be measured pre-dose and at the end of infusion.

n) 12 lead electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position.

o) Includes total IgE, absolute basophil and absolute blood eosinophil counts. Serum and plasma samples will be stored at -80°C for post hoc analysis of exploratory biomarkers.

p) Skin biopsies are optional and will only be obtained the sites in Germany.

q) [redacted] should be completed if the subject has a history of[redacted] at Screening.

r) Dose may be increased to 3 mg/kg at Dose 4, 5, and 6 at Day 85, 113, and 141 respectively if the UCT is <12, and/ or at the discretion of the Investigator in consultation with the Allakos Medical Monitor, but will stay at 1 mg/kg if UCT is ≥12 and if the Investigator in consultation with the medical monitor feels that the patient has received adequate symptom improvement.

s) During the physical exam the evaluating physician will also ask patients to rate the intensity of their atopic disease on a scale of 0–10; 0 (no symptoms) to 10 (worst possible symptoms).

Table 2 Schedule of Assessments for Extended Dosing

	Screening Period	Treatment Period		Follow-up Period
	Visit 1	Visit 2	Visits 3-13	Visit 14
	Ext Day -21 to Ext Day -14	Ext Day 1	Ext Days 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309 (± 2)	Ext 365 (± 3) or ET 28 (± 3) Days After Last Dose
	Week -3 to -2	Week 0	Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44	Week 52
Description	**Screening**	**Baseline[a]/Dosing**	**Dosing**	**End of Study/ET**
Informed consent	x			
Eligibility assessment/ confirmation	x	x		
Demographic data	x			
Medical history	x			
Prior CU treatment	x			
Prior/concomitant medication	x	x	x	x
Rescue medication use		x	x	x
Study drug administration[b]		x	x	
Patient diary	x	x	x	x
[redacted]		x	x	x
UCT		x	x	x
[redacted]		x	x	x
[redacted]		x	x	x
CBC with differential[e]		x (pre-dose)	x	x
Blood chemistry		x (pre-dose)	x (pre-dose)	x
Blood sample for PK[f]		x (pre-dose)		x
Blood sample for ADA[g]		x (pre-dose)	x (pre-dose)	x
Serology[h]	x			
Urinalysis[i]		x		x

Table 2 Schedule of Assessments for Extended Dosing (continued)

	Screening Period	Treatment Period		Follow-up Period
	Visit 1	Visit 2	Visits 3-13	Visit 14
	Ext Day -21 to Ext Day -14	Ext Day 1	Ext Days 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309 (± 2)	Ext 365 (± 3) or ET 28 (± 3) Days After Last Dose
	Week -3 to -2	Week 0	Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44	Week 52
Description	Screening	Baseline[a]/Dosing	Dosing	End of Study/ET
Urine pregnancy		x	x	x
Serum pregnancy[j]	x			
Stool for ova and parasite	x			
Physical examination[c]	x[k]	x[l]	x[l]	x[k]
Vital signs[m]	x	x	x	x
Weight	x	x	x	x
12-lead ECG[n]	x			x
Adverse events[o]		x	x	x

Table 9 Notes Ext: Extended

a) Baseline is defined as up to 48 hours prior to first dose.

b) AK002 will be administered as a single peripheral IV infusion at a dose of 0.3 mg/kg (Dose 1) on Extended Dosing Day 1. If well tolerated, the dose will be increased to 1 mg/kg on Extended Dosing Days 29 (Dose 2) and 57 (Dose 3). The dose will be increased to 3 mg/kg for doses 4 through 12 The Investigator in consultation with the Medical Monitor can up dose to 3 mg earlier than dose 4 if needed. (Extended Dosing Days 85, 113, 141, 169, 197, 225, 253, 281, and 309, respectively) if the subject has a UCT score <12, and/or at the discretion of the Investigator in consultation with the Allakos Medical Monitor. If the UCT score is ≥12, and if the Investigator in consultation with the Medical Monitor feels that the subject has received adequate symptom improvement, the subject will remain at the 1 mg/kg dose. All doses will be administered over a period of approximately 4 hours, although the duration of infusion and the rate at which the infusion is given may be adjusted based on Investigator discretion. Please refer to the Pharmacy Manual for detailed instructions on preparations, administration, and infusion rate. The Investigator in consultation with the Medical Monitor may increase the dose to 6 mg/kg and then to 10 mg/kg if they think that the patient has not received benefit from the lower doses.

c) During the physical exam the evaluating physician will also ask subjects to rate the intensity of their atopic disease on a scale of 0–10; 0 (no symptoms) to 10 (worst possible symptoms).

d) Subjects should complete the [redacted] on a weekly basis. On weeks where a clinic visit is not scheduled, the [redacted] should be completed at home.

e) Blood for CBC with differential, including absolute blood eosinophil and basophil counts, will be obtained just prior to each infusion, 1 hour after the end of each infusion, and on Extended Dosing Day 365 (or ET).

f) If possible, blood for PK analysis should be obtained from the arm not used for study drug infusion.

g) ADA will be obtained Visits 2, 3, 5, 8 and 10. An unscheduled ADA blood sample may be obtained if an immunogenicity-related AE is suspected.

h) Serology at screening includes hepatitis B surface antigen, hepatitis C antibody, hepatitis B core antibody, and human immunodeficiency virus.

i) At screening, include urine drug screening (alcohol, amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine, methadone, methaqualone, opiates, phencyclidine) and urine cotinine tests.

j) Blood for serum pregnancy test at Screening Visit.

k) A complete PE will be performed by either the Investigator or designee as noted in Section **Error! Reference source not found.**.

l) A symptom-directed PE, including assessments of possible infusion site reactions, will be performed by the Investigator or designee as needed.

m) Vital signs, including supine systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate, will be taken after the subject has been in the supine position for ≥5 minutes and before any blood draw. On AK002 dosing days, vital signs will be measured pre-dose and at the end of infusion.

n) 12 lead ECGs must be recorded after 10 minutes rest in the supine position.

o) All AEs identified, whether serious or non-serious, will be recorded in the eCRF until Day 365 (± 3) or ET 28 (± 3) days after last dose.

3.2 Study Treatment

3.2.1 Treatment, Dose, and Mode of Administration

AK002 will be administered as an intravenous (IV) infusion at a dose of 0.3 mg/kg on Study Day 1. If well tolerated, the dose will be increased to 1 mg/kg on study Day 29 and Day 57 (±2 days). Dose will be increased to 3 mg/ kg on Days 85, 113 and 141 if the UCT score is <12 or at the discretion of the Investigator in consultation with the Allakos Medical Monitor and if the 1 mg/kg dose was well tolerated. If the UCT score is ≥12 and if the Investigator in consultation with the medical monitor feels that the patient has received adequate symptom improvement, then the patient will continue to receive 1 mg/kg dose. The amount of AK002 to be administered will be calculated based on the patient's body weight determined within 24 hours of each infusion.

Subjects in the CholU, UF, and CSU-XOLAIR® failure cohorts at the select sites will be alllowed to participate in the Extended Dosing part of the study if they meet the symptom criteria below: subjects must have a baseline (Day 1) UCT of ≤5 and a week 22 (Day 155) UCT of ≥12 (Complete Response). They must have a UCT of ≤5 between Day 155 and Day 309 (i.e., within 6 months from last dose). All subjects that decide to receive the extended dosing will start with a dose of 0.3 mg/kg, followed by possible dose increases to 1 mg/kg and 3 mg/kg for subsequent infusions. The Investigator in consultation with the Medical Monitor may increase the dose to 6 mg/kg and then to 10 mg/kg if they think that the patient has not received benefit from the lower doses.

3.2.2 Duration of Study

Total subject duration on the main study is approximately 32 weeks.

- Screening phase: 4 weeks
- Treatment phase: 20 weeks
- Follow up after Treatment phase: 8 weeks

For subjects who participate in the Extended Dosing part (select sites) of the study, their total extended duration is up to 52 weeks.

- Screening: 3 weeks
- Treatment phase: up to 44 weeks (12 infusions)
- Follow up phase: 8 weeks

3.3 Methods of Assigning Subjects to Treatment Group

All subjects will receive the same treatments. Approximately 48 subjects who meet all of the inclusion but none of the exclusion criteria will be enrolled and assigned a patient ID number (PID). The PID is comprised of study number (first 3 digits), site number (second 3 digits), disease

cohort (the 7th digit), and order of enrollment (the last 2 digits). The disease cohorts and the approximate sample sizes are defined as follows.

1 = Cholinergic Urticaria (CholU) (n=12)
2 = Urticaria Factitia (UF) (n=12)
3 = Chronic Spontaneous Urticaria Xolair Naïve (CSU-XN) (n=12)
4 = Chronic Spontaneous Urticaria Xolair Failure (CSU-XF) (n=12)

3.4 Blinding

Not applicable, as the study is open label.

3.5 Hypotheses

There are no formal tests of hypotheses in this study.

3.6 Determination of Sample Size

The planned sample size of approximately 48 subjects is based on common practice in early phase, proof-of-concept studies.

3.7 Changes to Analyses Planned in the Protocol

None.

3.8 Efficacy Assessments

A number of cohort-specific efficacy variables, including patient-reported outcome (PRO) instrument, will be assessed during the study. Subjects will be administered only with the instruments relevant to their condition (see

Table 3).

Table 3 Patient-Reported Outcome Instruments for Efficacy Assessment

Patient Reported Outcome Instrument	Disease Cohort		
	CholU	UF	CSUs
Urticaria Control Test (UCT) (monthly)	x	x	x
Urticaria Patient Daily Diary (UPDD)			
• [redacted]			
• UAS7 (itch and hives)	x	x	x
[redacted]			
[redacted]*	x	x	x
[redacted]	x	x	x

* If applicable. All patients who have a history of [redacted] at Screening will complete the [redacted] and the [redacted]

3.8.1 Urticaria Control Test

The Urticaria Control Test (UCT) (Appendix B.2) is a 4-item questionnaire for assessing CU disease activity retrospectively over the previous 4 weeks. Each item is rated on a Likert-scale (0 = very often to 4 = not at all) and a total score (the sum of all item scores) is calculated (range, 0 to 16; higher scores indicate better disease control; scores ≥12 are consistent with well-controlled disease). The UCT total score will not be calculated when ≥1 item within the questionnaire is missing.

CR, CMR, and DC for UCT are defined in Section 4.

3.8.2 [redacted]

[redacted] (Appendix B.3) is a questionnaire for the last 2 weeks. It comprises [redacted] each that are scored from [redacted] relating to overall functioning (including work, physical well-being, leisure and social activities), sleep, itching/embarrassment, mental status, swelling/eating, and limits in look (limitations in choice of clothing or cosmetics used due to [redacted]). Total scores range from 0 to 100, with higher scores indicating worse [redacted]. The [redacted] total score will not be calculated when >14 items within the questionnaire are missing. The [redacted] domain scores as well as the total score are calculated by using the following formula:

$$\frac{\sum_{nonmissing\ items} \text{Item Score Reported}}{\sum_{nonmissing\ items} \text{Max Possible Item Score}} \times 100$$

3.8.3 [redacted]

[redacted] (Appendix B.4) is a questionnaire for the last 2 weeks. The total score is calculated from the [redacted] scores. Score will be calculated using the formula described in Section 3.8.2.

3.8.4 [redacted]

[redacted] (Appendix B.5) is a questionnaire for the last 7 days. It comprises [redacted] items. Total score will be calculated and converted to the scale of 0-100 using the formula described in Section 3.8.2.

3.8.5 [redacted]

[redacted] (Appendix B.6) is a questionnaire for the last 4 weeks. It comprises [redacted] items and will be grouped into [redacted] domains. The domain and total scores will be calculated and converted to the scale of 0-100 using the formula described in Section 3.8.2.

3.8.6 [redacted]

[redacted] (Protocol Appendix B.7) is a questionnaire for the last 7 days. It is a [redacted]-item [redacted]-specific health-related quality of life measure. An overall score will be calculated as well as for the following domains: Symptoms and Feelings, Daily Activities, Leisure, Work and School, Personal Relationships, Treatment. The minimally important difference of the overall [redacted] score for patients with CSU has been estimated to be [redacted]. The total score is the sum of all item scores, ranging from [redacted] with higher score for more impairment. The total score will not be calculated if >1 item score is missing.

3.8.7 Urticaria Patient Daily Diary

All patients were provided with a Urticaria Patient Daily Diary (UPDD) to complete daily. The UPDD has 3 separate versions; one for CholU patients (including itch, hives and elicitors) (Appendix B.1.1), one for UF patients (including redness, hives, and itch) (Appendix B.1.2), and one for CSU patients (including itch and hives) (Appendix B.1.3). Complete Response (CR) and Clinically Meaningful Response (CMR) are defined in Section 4.

3.8.8 [redacted]

[redacted] is a 7-day sum of [redacted], where [redacted] respectively, and [redacted] is the intensity of the [redacted] (Appendix B.1.1). The symptom score [redacted] ranges from [redacted]

[redacted] using the numeric rating scale (NRS). The [redacted] ranges from [redacted] and the values are as follows:

[redacted]

The 7-day sum is calculated as 7× (times) mean of all available daily [redacted] scores.

The [redacted] will be set to missing when no UAS scores are recorded for a given 7-day period. CR and CMR are defined in Section 4.

3.8.9 [redacted]

[redacted] is a 7 day sum of the daily [redacted] and the daily [redacted] score (Appendix B.1.3, Question 1).

The daily [redacted] score ranges from [redacted] on NRS. The possible range of the weekly CR and CMR are defined in Section 4.

The [redacted] score is calculated as 7× mean of all available daily [redacted] scores.

The [redacted] will be set to missing when no [redacted] scores are recorded for a given 7 day period. [redacted] and [redacted] Score

[redacted] are derived by adding up the daily [redacted] and [redacted] scores respectively (Appendix B.1.3, Question 1) for 7 days a week throughout the study. The [redacted] score ranges from [redacted] and the [redacted] score ranges from [redacted] using the numeric rating scale (NRS).The possible range of the weekly score is [redacted]. The [redacted] and the [redacted] score is calculated as 7× mean of all available daily [redacted] and [redacted] scores respectively.

Missing diary entries will be handled in the same way as described for the Weekly [redacted].

3.8.10 Additional Measures for Disease Activity and Functional Status

The following assessments will be administered to assess disease activity and functional status. The assessments will be cohort-specific.

- [redacted] (Appendix B.8) will be used to determine disease activity in subjects with recurrent [redacted], independent of its underlying causes. Subjects will use the [redacted] for daily documentation of [redacted] episodes including duration, severity and impact on daily functioning and appearance.

- The [redacted] and [redacted] scoring systems will be used to assess disease activity.

3.8.11 Skin Biopsies (optional and only in certain sites)

The assessments of the skin biopsies will include:

- Haematoxylin and eosin (H&E) and giemsa stains to assess the number of MCs and eosinophils in the skin
- Other potential post hoc analyses to investigate the mechanism of action of AK002

3.9 Safety Assessments

3.9.1 Physical Examination

Physical examinations will be conducted at Visits 1 to 7. Clinically significant findings will be reported as adverse events.

3.9.2 Vital Signs, Height and Weight

Vital signs are measured at all visits. It includes blood pressure (BP), body temperature, heart rate, and respiratory rate. Height (cm) and body weight (kg) are also measured at the same visits.

3.9.3 Laboratory Tests

Laboratory tests will be collected at all visits. The tests include hematology, chemistry and CBC with differential, and urinalysis panels. Laboratory values will be categorized according to the appropriate laboratory reference ranges.

3.9.4 Anti-Drug-Antibodies

Blood will be collected for the determination of anti-drug antibodies (ADA) before the first dose at Visit 2 and at all the following visits. An unscheduled blood sample for ADA may be obtained if a related adverse event suspected of being associated with immunogenicity occurs.

3.9.5 Electrocardiogram

Standard 12 lead electrocardiograms (ECGs) will be recorded at all visits.

3.9.6 Pregnancy Testing

Serum pregnancy test (post menopause FSH) will be done only at Baseline. Urine pregnancy (for all women of child-bearing potential) will be done at Visits 2 to 7.

3.9.7 Tolerability/Acceptability

Adverse events leading to study drug discontinuation will be collected.

3.9.8 Medical History and Adverse Events (AEs)

AEs that occur on/after signing Informed Consent Form (ICF) will be recorded on the AE CRF. Medical history and AEs will be coded for preferred term (PT) and system organ class (SOC) using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. AEs are evaluated by the investigators for seriousness, causality, and severity.

3.9.9 Prior, Concomitant, and Prohibited 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 and medications taken on or after Study Day 1 will be considered as concomitant medications. Prior and concomitant medications will be coded using WHO Drug Dictionary (WHODD March 2018 release) for Preferred Term (PT) and Anatomical Therapeutic Chemistry (ATC) classification.

Prohibited medications include, but are not limited to,

- Omalizumab
- H2-antihistamines
- Routine (daily or every other day during 5 or more consecutive days) doses of systemic corticosteroids
- Routine (daily or every other day during 5 or more consecutive days) doses of systemic hydroxychloroquine
- Routine (daily or every other day during 5 or more consecutive days) doses of methotrexate, cyclosporine A, cyclophosphamide, tacrolimus and mycophenolate mofetil
- Intravenous immunoglobulin G
- Plasmapheresis
- Regular (daily or every other day) doxepin (oral)
- Inactive vaccination
- Live attenuated vaccine
- Leukotriene Antagonists

4. Definitions

Table 4 Terminology and Definition

Terminology	Definition
Study Medication/Drug (SM)	AK002 administered by IV infusion.
Study Day	The first dose date (Day 1) is defined as the date on which a subject took the first dose of study medication (SM). Other study days are defined relative to Study Day 1. For visits prior to the first dose of the SM, Study Day is calculated as Visit Date – Day 1. For visits after the first dose, Study Day is calculated as Visit Date – Day 1 +1.
Enrolled	Subject who has signed informed consent, met all eligibility criteria at Screening, and having received the first dose of the study drug.
Completer for the Study	Subject who completes End of Study visit
Baseline	Baseline is defined as the non-missing value collected most recent to and before the time of the very first dose of the SM.
Prior Medication	Medication collected on the Prior/Concomitant Medication CRF, with start date prior to Study Day 1.
Concomitant Medication	Medication collected on the Prior/Concomitant Medication CRF, with end date on/after Study Day 1.
Treatment-emergent	Adverse events with onset date on or after the start of first study drug administration.
UCT Response (all CU subjects)	UCT score ranges from 0 to 16. CR is UCT score ≥12 AND an increase from baseline in UCT score of ≥3 points. CMR is an increase in UCT score of ≥3 points. DC is UCT score ≥12. An increase from baseline in UCT score of ≥3 points is also regarded as the minimally clinically important difference.
UAS7 Response (CSU subjects)	Weekly UAS7 ranges from 0 to 42. [redacted]
[redacted] Response (CholU subjects)	Weekly [redacted] score ranges from 0 to 168. [redacted]

5. Efficacy and Safety Variables

5.1 Primary Endpoint

1) The primary efficacy endpoint is the change in Urticaria Control Test (UCT) for each population (CSU-XN, CSU-XF, UF, and CholU). The UCT is a score for symptom control in chronic urticaria, from Day 1 (baseline) to Week 10 for subjects enrolled under Protocol Amendment 2.1 and Week 22 for all remaining subjects (i.e., those on study during Protocol Amendment 3). A change of the UCT score of 3 or more points is regarded as clinically relevant (minimal clinically important difference [MCID]). If Week 10 or Week 22 measures

are not available, they will be imputed with last observation carried forward method (LOCF). The data summary will include Week 10 and Week 22 derived from the available data and Week 10/LOCF and Week 22/LOCF derived from the available plus the imputed data.

5.2 Secondary Endpoints

1) Proportion of subjects with CR, CMR, and DC based on UCT (all patients) at all time points. Section 4 provides the definition of CR, CMR, and DC.

2) Change from baseline in disease activity as assessed by UAS7 at each week in CSU patients. If Week 10 or Week 22 measures are not available, they will be imputed with the last non-missing weekly UAS7 (LOCF). The data summary will include Week 10 and Week 22 derived from the available data and Week 10/LOCF and Week 22/LOCF from the available plus the imputed data.

5.3 Exploratory Endpoints

1) Change in [redacted] assessed by [redacted] at all post-baseline scheduled visits.

2) Proportion of CSU subjects with [redacted] each week.

3) Proportion of CSU subjects with [redacted] from Baseline in [redacted] at each week.

4) Proportion of CSU subjects with [redacted] from Baseline in [redacted] at each week.

5) Change from baseline in [redacted] as assessed by [redacted] at each week in CholU patients.

6) Change in weekly [redacted] over time.

7) Change in [redacted] at all post-baseline scheduled visits.

For weekly assessment, missing Week 10 and Week 22 scores will be imputed with LOCF.

5.4 PD Endpoint

1) Peripheral blood eosinophils.

5.5 Pharmacokinetic Endpoint

1) Blood samples will be analyzed for AK002 plasma concentrations and ADA.

5.6 Safety Endpoints

1) Safety endpoints include physical examination

2) routine safety laboratory assessments

3) vital signs

4) electrocardiogram (ECG)

5) urine safety, and

6) adverse event reporting (Visits 2–7).

6. Statistical Methods

6.1 General Methodology

All statistical analyses will be conducted using SAS Version 9.4 or later on the Microsoft® Windows Operating System.

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 and 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 of percentage calculations. Counts of zero in any category will be presented without percentage.

All endpoints will be summarized by the individual applicable cohorts (CholU, UF, CSU-XN or CSU-XF). Where appropriate, the summaries will also be carried out for all 4 cohorts combined.

Two-sided 95% confidence interval (CI) may be presented for the mean or percentage.

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

- Sample size (n, N) and number of missing responses (if displayed) – Integer
- Mean, CI – One more decimal place than reported/collected
- Standard deviation – Two more decimal places than reported/collected
- Median, other percentile, minimum, maximum – Same number of decimal places as reported/collected
- Ratio – two decimal places
- Percentage – one decimal place generally, or two decimal places for <0.1%

The data summaries will be accompanied by individual subject data listings. All data available from diary, questionnaires, eCRF, and external transfer (e.g., labs) will be listed and will include relevant and pertinent subject information, e.g. study day. The listings will be sorted in the order of Cohort and unique subject ID, and assessment name and assessment 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 Guidelines (ICH, 1996).

6.2 Visit Window and Unscheduled Assessments

There is no visit window for the by visit analysis. Data will be analyzed according to the visit they are associated with.

6.3 Adjustment for Covariates

Not applicable

6.4 Handling of Dropouts, Missing Data, and Data Discrepancies

Unless specified otherwise, in deriving the total (sum) score, the total score will be derived from all available item scores and scaled accordingly. For example, the total score of 7 items will be calculated as 7× (times) average of all available items score out of the 7 intended scores. In case the analysis week is extended to be >7 calendar days, the total score for the week will be calculated as 7 x average of all available daily scores for the analysis week. Also, scores will be set to missing when no scores are recorded for a given 7 day period. AEs with incomplete information for start or stop dates (i.e., either day or month is missing) will be considered treatment-emergent (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). AEs with missing relationship to study drug will be included in the "Related" category for the summary tables. AEs with missing severity will not be included in the summary table but will be footnoted.

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.

6.5 Interim Analysis

No interim analysis is planned.

6.6 Timing of Final Analyses

Data summary and statistical analysis will commence after all subjects have completed study Visit 7 (or discontinued prior to Visit 7) and the study database is cleaned and locked.

6.7 Multicenter Study

This is a multicenter study. The primary analysis will have all sites pooled. When appropriate, the by-country summaries may be presented. Response rates will be compared between the two participating countries, Germany and US.

6.8 Multiple Comparisons/Multiplicity Adjustment

Not applicable because no formal statistical analysis and hypothesis tests are planned.

6.9 Examination of Subgroups

If sample size allows, primary and key secondary efficacy variables may be summarized by subgroup to explore the heterogeneity of the treatment effect across subgroups. Subgroups that might be considered are:

- Gender (Male, Female)
- Age (<30, 30 to <55, 55+)

7. Statistical Analysis

7.1 Analysis Populations

The population of "all enrolled subjects" consists of all subjects who signed informed consent, met all eligibility criteria at Screening, and having received the first dose of the study drug.

7.1.1 Modified Intent-to-treat Population

The modified intent-to-treat (MITT) population will consist of all subjects who are enrolled, have received at least one dose of study drug and have at least one post-baseline assessment for the primary efficacy variable UCT.

7.1.2 Safety Population

The safety population will consist of all subjects who signed informed consent, met all eligibility criteria at Screening, and having received at least one dose of study drug.

7.1.3 Per-Protocol Population

The Per-Protocol (PP) population may be considered for the summary. The PP population will consist of all subjects from the MITT-population for whom no major protocol violations adversely affecting the data interpretation are reported.

7.2 Disposition of Subjects

Subjects (n and %) who completed or discontinued from the study will be tabulated by cohort and overall using all enrolled subjects. The primary reasons for study discontinuation will be included in the tabulation. The primary reasons may include 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 all Enrolled Subjects, MITT, Safety, and PP populations. A data listing will be presented for all enrolled subjects.

7.3 Protocol Deviations

Protocol deviations will include, but are not limited to

- Non-compliance with scheduled study visit
- Non-compliance with study treatment
- Prohibited medications
- Non-compliance with study inclusion or exclusion criteria
- Non-compliance with study assessment procedures

Protocol deviations will be reviewed and classified as major or minor based on their effect on the integrity of the study. 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.

7.4 Demographics and Baseline Subject Characteristics

Descriptive statistics of subject characteristics and baseline values will be presented by cohort and overall using the MITT and Safety populations.

All demographic and baseline characteristics will be included in the subject data listing.

7.5 Baseline Disease Characteristics

Summaries of baseline disease characteristics will be based on the Safety population.

Subject incidence (n and %) of medical history (and current medical condition present before signing the informed consent) will be tabulated by MedDRA System Organ Class (SOC) and Preferred Term (PT). Subject smoking habits will also be tabulated.

All baseline disease characteristics will be listed.

7.6 Treatments

7.6.1 Treatment Compliance and Extent of Exposure

Summaries of treatment compliance and exposure for AK002 and second generation of H1-antihistamine will be based on the safety population.

Duration of exposure is defined as the total number of days a subject is exposed to the study treatment. This will be calculated for each subject by taking the difference between the date of the last dose minus the date of the first dose, plus 1 (date of last dose – date of first dose +1).

Duration of Treatment exposure will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).

Subjects will be tabulated with n (%) by the number of doses they received.

7.6.2 Prior and Concomitant Medications

Prior and concomitant medications will be tabulated separately based on the Safety Population.

Number (n and %) of subjects taking at least one medication and the number (%) of subjects taking each medication at the WHODD PT 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, indication, route, and frequency, study day, and pertinent subject information.

A separate data listing will include subjects who received prohibited medications.

7.7 Efficacy Analyses

7.7.1 Primary Efficacy Analysis

The primary efficacy variable is the change from baseline in UCT score for each population (CSU-XN, CSU-XF, UF, and CholU). UCT score and its change from baseline will be summarized using descriptive statistics by study visit (Weeks 4, 8, 10, 12, 16 for subjects enrolled under Protocol Amendment 2.1 and Weeks 4, 8, 12, 16, 20, 22, 24, and 28 for subjects enrolled after Protocol

Amendment 3). A 95% CI for the mean change will be computed. The summaries will be provided for each cohort.

7.7.1.1 Per Protocol Analysis

This analysis will be conducted by repeating the primary analysis on the per protocol population.

7.7.1.2 Subgroup Analysis

The primary efficacy analysis will be conducted for the gender and age subgroups as defined in Section 6.9.

7.7.1.3 Secondary Efficacy Analyses

All summaries will be provided for each cohort.

1) Subjects achieving UCT CR and CMR will be tabulated with % of subjects for each visit. Subjects achieving a maximum of 0, 1, 2, 3, or 4 responses over the 8 post-baseline visits (subjects enrolled under Protocol Amendment 3) will also be tabulated. A 95% CI for the % responses will be calculated using the binomial distribution. Subjects achieving UCT DC will be similarly summarized.

2) Changes from baseline in UAS7 in CSU patients will be summarized similarly for each week the diary is collected. A 95% CI for the mean change will be reported. This analysis will also be carried out in the subgroup of CSU-XN patients with baseline UAS7 ≥16.

7.7.2 Exploratory Efficacy Analyses

1) Change from baseline score in [redacted] along with the visit score will be summarized descriptively with 95% confidence interval for each of the 4 cohorts. Where applicable, both total and domain scores will be summarized. This summary will be performed for all visits scheduled for assessments.

2) A cumulative distribution function (CDF) plot will be created by cohort for percent of patients who experience a maximum of no improvement, 1-point improvement, 2-point improvement, up to 30-point improvement in [redacted] total score. A table summarizing number and percent of patients will also be presented.

3) CSU subjects achieving [redacted] will be tabulated with % of subjects for each study week. Similarly, subjects achieving [redacted] ≤6 and subjects achieving ≥10 point decrease from baseline will be tabulated for each week.

4) CSU subjects achieving ≥5 point decrease from baseline in [redacted] and [redacted] will be tabulated with % of subjects for each study week.

5) Change from baseline in [redacted] subjects will be summarized descriptively at each week.

6) The daily [redacted] will be summarized for each subject at each week. The weekly average scores will be listed for all subjects.

7) Changes in [redacted] and [redacted] will be summarized at each study visit.

7.8 Pharmacodynamic Analysis

Eosinophil count from peripheral blood collected pre-dosing will be summarized by visit.

7.9 Pharmacokinetic Analysis

AK002 blood concentration will be summarized by the visit the samples are collected.

7.10 Safety Analyses

7.10.1 Adverse Events

Safety assessments will be based mainly on the nature, frequency, relationship, and severity of adverse events (AEs). AEs will be coded by primary system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. The treatment-emergent adverse events (TEAEs) 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 AEs are reported with the same preferred term, the AE of the strongest relation 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 TEAEs to include
  - Number (%) of subjects who reported at least one TEAE
  - Number (%) of subjects who reported at least one treatment-related TEAE
  - Number (%) of subjects who reported at least one severe TEAE
  - Number (%) of subjects who reported at least one serious TEAE
  - Number (%) of subjects who reported at least one TEAE leading to treatment discontinuation
- TEAEs by PT sorted by decreasing order of subject incidence in the combined cohort
- TEAEs by SOC and PT sorted alphabetically
- Study Drug-Related TEAEs by SOC and PT
- TEAEs Grade 2+ Severity by SOC and PT

- TESAEs by SOC and PT
- TEAEs leading to study drug discontinuation by SOC and PT

Select TEAEs of pain, tenderness, erythema/redness, induration/swelling, nausea/vomiting, diarrhea, headache, fatigue, and myalgia will be summarized with n and % by toxicity grade.

All AEs will be listed with onset/stop day, relationship to study drug, severity, action taken, and outcome. Pertinent subject information including cohort and demographics will also be included. Separate listings will be provided for TEAEs leading to study discontinuation and Treatment-emergent serious AEs (TESAEs).

7.10.2 Laboratory Test

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

Shift tables will be presented, in which, lab test results at baseline and post-baseline 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 the summary and shift tables will only use the planned/scheduled tests. However, both scheduled and unscheduled/repeat tests will be included in the data listing.

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

7.10.3 ECG

The investigator overall evaluation of normal, abnormal not clinically significant, and abnormal clinically significant ECG findings will be tabulated with number and % of subjects for each assessment visit.

Actual and change from baseline in PR, QRS, QT, RR, QTc, and HR will be summarized with descriptive statistics for each assessment visit.

Data listings will be presented for ECG parameters by visit. QTc meeting the criteria of >450 but ≤480, >480 but ≤500 or >500 msec for the actual value, or >30 msec or >60 msec increase from baseline will be identified.

7.10.4 Vital Signs 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 scheduled visit and time point. A data listing will include vital signs from all visits.

Other safety assessments will be listed.

8. Analysis Plan for the Extension Part of the Study

The extension part of the study will have the same conduct and data collection as for the main part of the study. A few exceptions are that the extension part (1) enrolls only patients meeting entry criteria from certain sites, (2) provides patients longer and flexible treatment (see 3.23.2.1), (3) eliminates some data collections, e.g., QoL instruments (see Table 1 and Table 2). The analysis for the extension study will virtually be the same as for the main study with some adjustment for the visit schedules. No separate analysis plan will be developed for this part of the study.

9. Validation

The Clinical Operations, Data Management and Biostatistics groups at Allakos will work with EDC/Data Management (DM) vendor to ensure that the data collected for the study are of the highest quality possible. The study monitor will be responsible for reviewing and verifying the accuracy of the data recorded on the electronic case report forms (eCRFs) direct 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 (TLFs) based on the clinical data is outsourced to Etera Solutions (Etera). Allakos seeks to ensure the quality of the reports provided by Etera in the form of TLFs passing a rigorous validation process involving the following processes:

- 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.

The entire set of TLFs will be checked for completeness and consistency prior to its delivery to Allakos.

10. References

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

11. Appendices

11.1 Appendix A: Exclusion Criteria for the Per Protocol Populations

The following criteria will be used to further exclude subjects from the PP population:

- Subject received incomplete dose of study drug.
- Subject received prohibited medication that could potentially confound the efficacy outcome.

11.2 Appendix B.1.1: Urticaria Patient Daily Diary for Patient with Cholinergic Urticaria

1) Did you do anything today that normally triggers symptoms?
   - No
   - Yes, with low intensity
   - Yes, with moderate intensity

- Yes, with high intensity
  - What exactly?

2) Did you have hives today?
   - No
   - Yes, with low intensity
   - Yes, with moderate intensity
   - Yes, with high intensity

3) Did you have any itching today?
   - No
   - Yes, with low intensity
   - Yes, with moderate intensity
   - Yes, with high intensity

4) How would you rate your symptoms overall today?
   - Mild, easy to tolerate
   - Moderate, quite noticeable, certain limitations
   - Very intense, very noticeable, considerable limitations

5) Have you taken your daily tablet of antihistamines in the last 24 hours?
   - No _____ Yes _____

6) Have you taken any rescue medication in the last 24 hours?
   - No _____ Yes _____

   How many
   - 1 tablet, 2 tablet, 3 tablet

7) Have you taken any other medications besides your regular medications in the last 24 hours (for example, pain tablets, cortisone, …)?
   - No _____ Yes _____

   How many
   - 1, 2, …, 10

   Medication
   - Drug taken: Today _____ Yesterday _____ Another Date_____
   - Medication name _____ Indication _____ Dosage (mg) _____
     How often during the study _____

11.3 Appendix B.1.2: Urticaria Patient Daily Diary for Patient with Urticaria Factitia

1) Were you free of your urticaria factitia symptoms today?
   - No ___ Yes ____

2) Please rate your urticaria factitia symptoms in the last 24 hours.
   - VAS (0 means no symptoms; 10 means maximum symptoms)

3) Please rate your symptoms of redness and hives in the last 24 hours.
   - Redness VAS (0 means no symptoms; 10 means maximum symptoms.)
   - Hives VAS (0 means no symptoms; 10 means maximum symptoms.)

4) How severe was the average and maximum itching caused by the urticaria factitia in the last 24 hours?
   - Average itching VAS (0 means no symptoms; 10 means maximum symptoms.)
   - Maximum itching VAS (0 means no symptoms; 10 means maximum symptoms.)

5) For how many hours did you have itching caused by urticaria factitia in the last 24 hours?
   - <3 hours ____ 3–12 hours ____ >12 hours ____

6) How much did the disease impair your quality of life in the last 24 hours?
   - Not at all ___ Somewhat ____ Much ____ Very much ____

7) How often did you avoid stimuli in the last 24 hours that are knows to result in symptoms?
   - Not at all ____ Somewhat ____ To a great extent ____ Completely ____

8) Have you taken your daily tablet of antihistamines in the last 24 hours?
   - No ____ Yes ____

9) Have you taken rescue medication in the last 24 hours?
   - No ____ Yes ____

   How many
   - 1 tablet ____ 2 tablet ____ 3 tablet ____

10) Have you taken any other medications besides your regular medications in the last 24 hours (for example, pain tablets, cortisone, ….)
   - No ____ Yes ____

   How many
   - 1 __, 2__, …., 10 __
   - Drug taken: Today _____, Yesterday _____, Another Date_____
   - Medication name _____, Indication _____, Dosage (mg) _____,

   How often during the study _____

11) Please indicate if provocation test was performed
   - Yes ___ No ___

   Indicate if hives and/or redness occurred 10 minutes after provocation, and how severe your itching was.
   - Hives: Yes ___ No ___
   - Redness: Yes ___ No ___
   - Itching: NRS: 0 (no itching), 1, 2, …, 10 (max itching imaginable)

11.4 Appendix B.1.3 Urticaria Patient Daily Diary for Patients with Chronic Spontaneous Urticaria

Diary of Symptoms

1) Symptoms and medication use in the last 24 hours

- Hives: None ___ <20 ____ 20–50 _____ >50 _____
- Itching: None ___ Mild ___ Moderate ___ Severe ___

2) Did you use the daily antihistamine tablet in the last 24 hours?

- No ___ Yes ___

3) Did you use any rescue medication in the last 24 hours

- No ___ Yes ___

How many

- 1 tablet ___ 2 tablets ___ 3 tablets ___

4) Did you use any other medications in the last 24 hours

- No ___ Yes ___

How many

- 1 __, 2 __, …, 10
- Drug taken: Today _____, Yesterday _____, Another Date_____
- Medication name _____, Indication _____, Dosage (mg) _____

How often during the study _____

11.5 Appendix B.2: Urticaria Control Test

The Urticaria Control Test (UCT) is a simple 4-item tool. A score between 0 and 4 is assigned to every answer option. Subsequently, the scores for all 4 questions are summed up. Accordingly, the minimum and maximum UCT scores are 0 and 16, with 16 points indicating complete disease control. UCT questions and the score for each answer option are as follows.

1) How much have you suffered from the physical symptoms of the urticaria (itch, hives (welts) and/or swelling) in the last four weeks?

O very much	O much	O somewhat	O a little	O not at all
(0 points)	(1 point)	(2 points)	(3 points)	(4 points)

2) How much was your quality of life affected by the urticaria in the last 4 weeks?

O very much	O much	O somewhat	O a little	O not at all
(0 points)	(1 point)	(2 points)	(3 points)	(4 points)

3) How often was the treatment for your urticaria in the last 4 weeks not enough to control your urticaria symptoms?

O very much	O much	O somewhat	O a little	O not at all
(0 points)	(1 point)	(2 points)	(3 points)	(4 points)

4) Overall, how well have you had your urticaria under control in the last 4 weeks?

O very much	O much	O somewhat	O a little	O not at all
(0 points)	(1 point)	(2 points)	(3 points)	(4 points)

Cut off-value of ≤11 is usually recommended (<12: poorly controlled urticaria, ≥12: well controlled urticaria).

Reference: www.moxie-gmbh.de

11.6 Appendix B.3 [redacted]

[redacted]

[redacted]

[redacted]

11.7 Appendix B.4: [redacted]

[redacted]

[redacted]

11.8 Appendix B.5: [redacted]

[redacted]

[redacted]

Reference: [redacted], Version 25 Jul 2017.

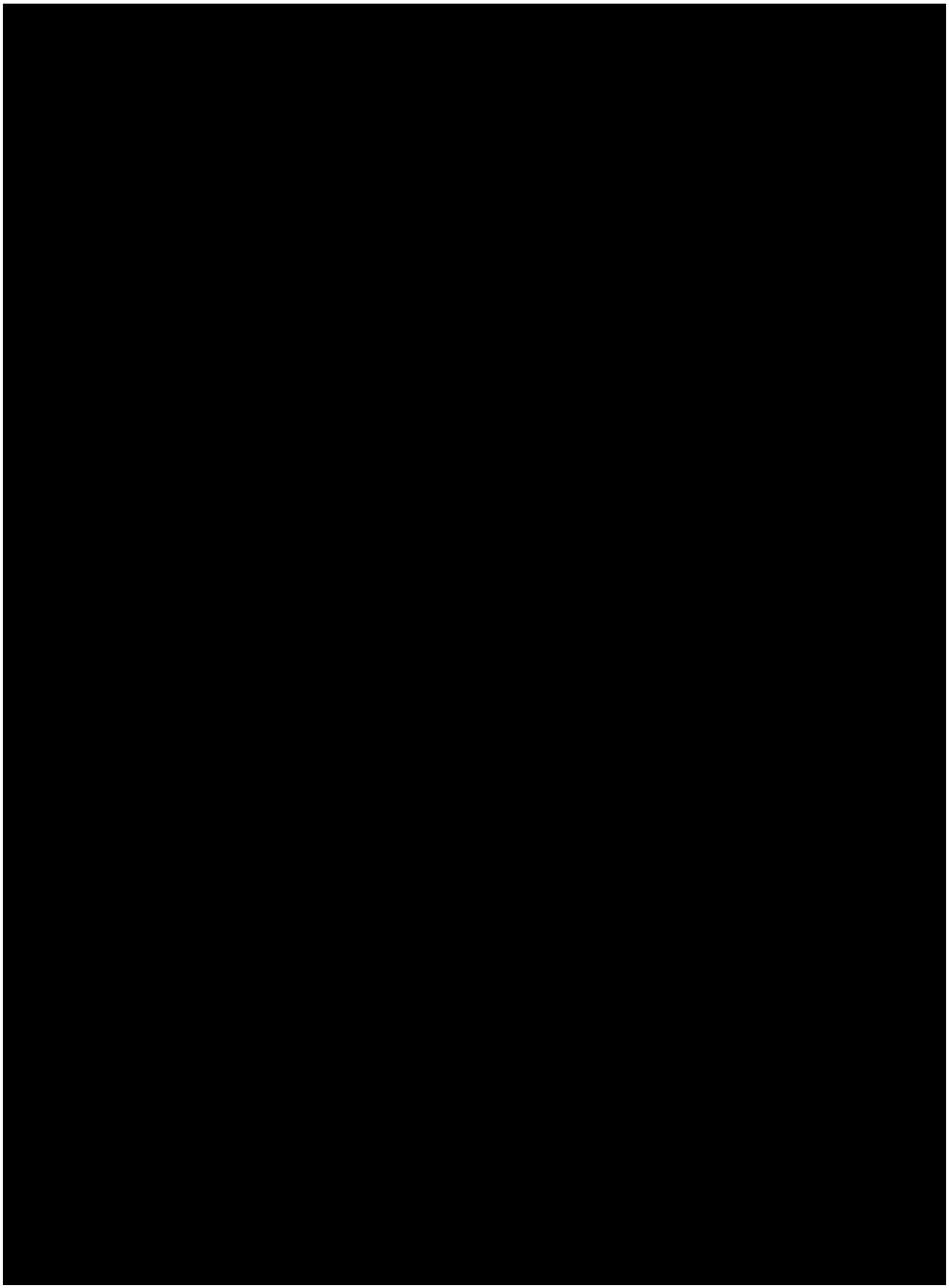
11.9 Appendix B.6: [redacted]

[redacted]

[redacted]

11.10 Appendix B.7: [redacted]

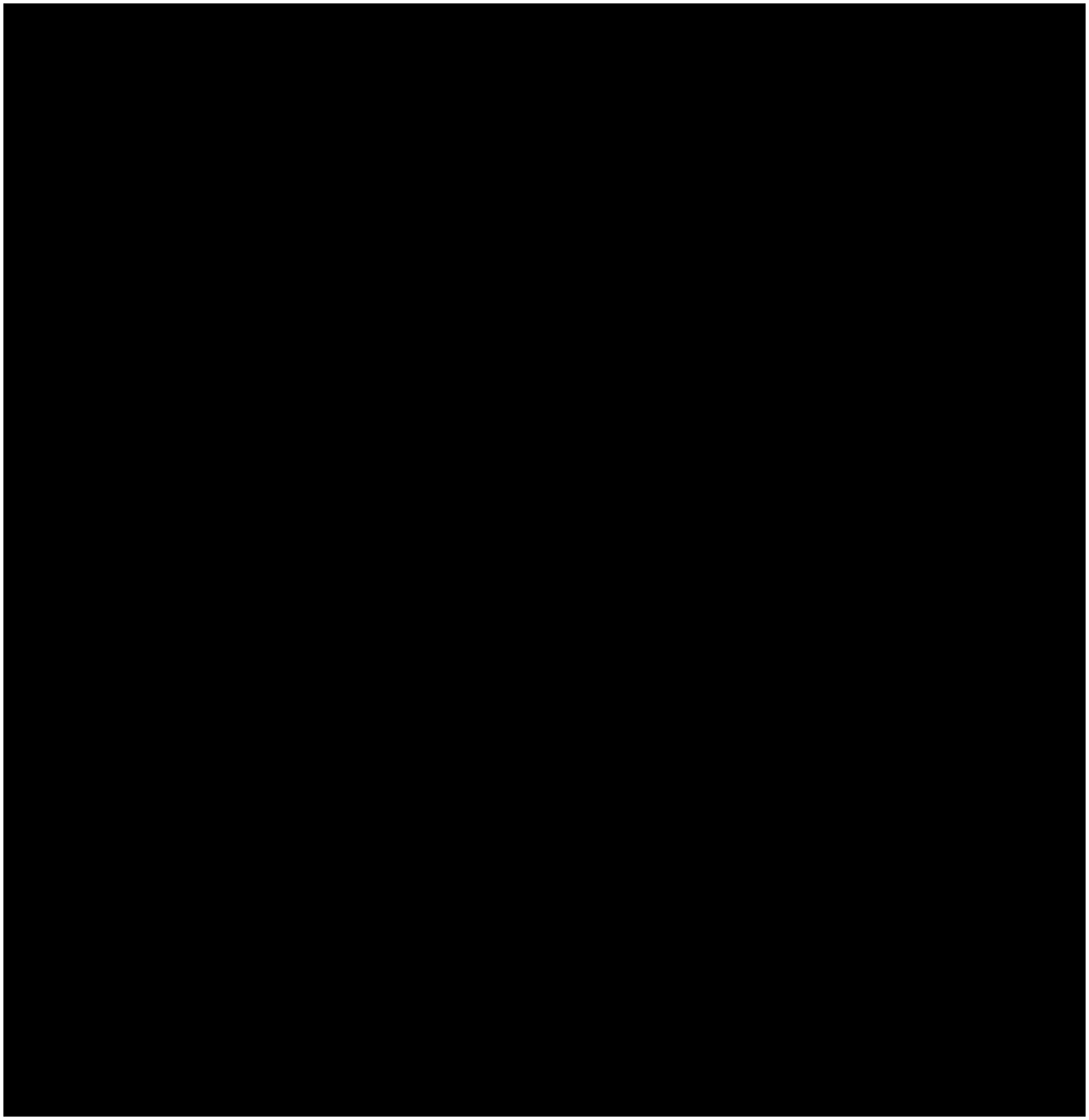
[redacted]



[redacted]

11.11 Appendix B.8: [redacted]

[redacted]



11.12 Appendix C: List of Tables, Listings, and Figures

Table No.	Title	Population

Listing No.	Title	Population

Figure No.	Title	Population

11.13 Appendix D: Table and Listing Shells