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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Clinical Research Protocol AK002-006

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

Short Title: CURSIG (Chronic Urticaria Response to AK002 (Siglec-8)

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Approval:

[redacted]

[redacted], MD, PhD, [redacted]

4 DEC 2018

Date

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Investigator Protocol Agreement

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

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Investigator:

Printed Name: _____

Signature: _____

Date: _____

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List of Abbreviations

[redacted]	[redacted]
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
[redacted]	[redacted]
AH	Antihistamine
BP	Blood pressure
CFR	Code of Federal Regulations
CholU	Cholinergic Urticaria
[redacted]	[redacted]
[redacted]	[redacted]
CINDU	Chronic Inducible Urticaria
CIU	Chronic Idiopathic Urticaria
CRF	Case Report/Record Form
CSU	Chronic Spontaneous Urticaria
CTCAE	Common Terminology Criteria for Adverse Events
CU	Chronic Urticaria
[redacted]	[redacted]
[redacted]	[redacted]
ECG	Electrocardiogram
ET	Early Termination
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HbsAg	Hepatitis B surface antigen
HIPAA	Health Information Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IRB	Institutional Review Board
IRR	Infusion-Related Reaction(s)
[redacted]	[redacted]
IV	intravenous administration
MC	Mast cell

MCID	Minimal Clinical Importance Difference
MedDRA	Medical dictionary for regulatory activities
NaCl	Sodium chloride
NCI	National Cancer Institute
NOAEL	No-observed-adverse-effect level
PCE	Pulse-Controlled Ergometry Test
PID	Patient Identification Number
PP	Per-Protocol population
PT	Preferred Term
QOD	Every other day
QoL	Quality of Life
RBC	Red blood cell(s)
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	subcutaneous administration
[redacted]	[redacted]
SOC	System Organ Classification
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
VAS	Visual Analog Scale
WBC	White blood cells(s)
WHO	World Health Organization

1. Protocol Synopsis

Study Title	An Open-Label, Pilot Study to Assess the Efficacy and Safety of AK002 (Siglec-8) in Subjects with Antihistamine-Resistant Chronic Urticaria
Short Title	**CURSIG** (**C**hronic **U**rticaria **R**esponse to AK002 (**Sig**lec-8))
Rationale	Chronic urticaria (CU) is a skin condition, which is characterized by transient pruritic wheal-and-flare-type skin reactions and, in some subjects, the occurrence of angioedema. About 1% of the population in Europe has chronic or recurrent urticaria (Hellgren, 1972). Subjects with CU are often impaired in their quality of life, with negative effects on sleep, daily activities, school/work life, and social interactions. Therefore, the current guidelines of the European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA^2LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) state that the aim of treatment for all types of urticaria is to achieve complete symptom relief. The current treatment guidelines for the management of all forms of urticaria recommend the use of non-sedating oral H1-antihistamines as first-line therapy. In more than 50% of subjects, symptoms persist with standard dosing of antihistamines. In antihistamine-refractory subjects with chronic spontaneous urticaria (CSU), the only currently licensed treatment is omalizumab, a monoclonal anti-IgE antibody. In subjects with chronic inducible urticaria (CINDU) including cholinergic urticaria (CholU) and urticaria factitia (UF), no other licensed drugs are available, and subjects often need to be treated with omalizumab, cyclosporin, or other off-label drugs. In double-blind placebo-controlled studies in selected antihistamine-refractory subjects, omalizumab has been shown to be very effective in the treatment of CSU and is recommended as third-line therapy if symptoms persist with 4-fold antihistamines. However, some CSU subjects continue to have symptoms despite omalizumab treatment or do not respond at all to omalizumab treatment. Approximately 60–65% of omalizumab patients continue to experience symptoms despite treatment, so there clearly is a need for new and better treatments (Saini, 2015). Furthermore, omalizumab is not licensed for the treatment of CINDU. There is a significant unmet need for new targeted therapeutic options for subjects with CSU and CINDU.
Study Design/Phase	This is an open-label, proof-of-concept study.
Objectives	To assess the effects of AK002 on symptom control in subjects with chronic urticaria. CU subjects will document triggers and symptoms (wheals, pruritus, etc.), as well as quality of life (QoL), before, during and after treatment. Subjects will also be subjected to standardized provocation tests and assessment of symptom development.

Primary Objective	To assess the efficacy of AK002 on symptoms in subjects with CU (change in urticaria control test [UCT] score).
Secondary Objectives	The efficacy, safety and pharmacodynamics of AK002 on urticaria symptoms, QoL, provocation testing, and histological criteria. The effects of AK002 in CU subjects will be assessed through the following evaluations: 1) Safety and tolerability (adverse events, laboratory safety tests etc.) 2) Disease activity scores (UAS7, [redacted]) 3) [redacted] 4) Number of symptom-free days 5) Use of rescue medication (up to 3 sgAH tablets/day) 6) Effects on [redacted] 7) Number of [redacted] 8) [redacted] 9) Changes in trigger thresholds (in CINDU, including CholU) 10) Rate of [redacted] (UCT, [redacted] 11) Serum levels of potential biomarkers of disease activity and treatment responses 12) Rates of relapse and sustained response during the follow-up period
Endpoints	
Primary Endpoint	The primary endpoint is the change in Urticaria Control Test (UCT), a score for symptom control in chronic urticaria, from baseline to Week 22 in CU subjects after treatment with AK002. A change of the UCT score of 3 or more points is regarded as clinically relevant (minimal clinically important difference [MCID]).
Other Endpoints	1) Safety of subjects treated with AK002: This includes physical examination, routine safety laboratory assessments, vital signs, electrocardiogram (ECG), urine safety, and adverse event reporting (Visits 2–10) 2) Change in disease activity as assessed by UAS7 and/or [redacted] from Baseline to Visits 3, 5, 8, and 10 3) Change in number of symptom-free days per week (patient diary-based CSU score; wheals, flares, itch, avoidance behavior) from Baseline to Visits 3, 5, 8, and 10

Other Endpoints cont.	4) Change in [redacted] assessed by [redacted] from Baseline to Visits 3, 5, 8, and 10 5) Change in number of intake of rescue medication from Baseline to Visits 3, 5, 8, and 10 6) In case of [redacted], change in [redacted] from Visit 2 to Visits 3, 5, 8, and 10, as assessed by [redacted] 7) Change in number of [redacted] from Baseline to Visits 3, 5, 8, and 10 8) Change in [redacted] from Baseline (Day 1) to Visits 3, 5, 8, and 10 9) Changes in trigger threshold from Baseline (Day 1) to Visits 3, 5, 8, and 10, as assessed by Pulse Controlled Ergometry Test (PCE) FricTest®, as applicable 10) Rates of complete response, partial response, and non-response based on UCT, [redacted], trigger thresholds (where applicable), and QoL from Baseline to Visits 3, 5, 8, and 10 11) Serum levels at baseline (Day 1) and change from Baseline to Visits 3, 5, 8, and 10 of serum levels of potential biomarkers in AK002-treated subjects (e.g., tryptase, eosinophils, total IgE, basophils, eosinophil cationic protein) 12) Rates of AK002-treated subjects with relapse, rebound, sustained treatment effects at Visit 7
Study Drug	**AK002** (Siglec-8 inhibitor)
Dose and Route of Administration	Up to 6 doses of AK002 will be given over the course of the study. AK002 will be administered as an intravenous (IV) infusion at a dose of 0.3 mg/kg given over a period of approximately 4 hours on study Day 1 (Dose 1). If well tolerated, dose will be increased to 1 mg/kg, given over a period of 4 hours on study Day 29 (Dose 2) and Day 57 (Dose 3) (±2 days). For Doses 4, 5, and 6 on Day 85, Day 113, and Day 141, respectively, dose will be increased to 3 mg/kg if patient has UCT score of <12, and/ or at the discretion of the Investigator in consultation with the Allakos Medical Monitor. If the UCT score ≥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. Subjects in the CholU, UF, and CSU-XOLAIR® (omalizumab) failure cohorts who received all 6 infusions of AK002, were followed at least through Day 155, and demonstrated severe symptoms of urticaria following the last dose of treatment will be allowed the option to receive extended dosing with up to 12 additional doses of AK002 (see Appendix 2). They will have to be treated with extended dosing within 6 months of last dose.

Dose and Route of Administration cont.	All subjects that decide to receive 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. The amount of AK002 to be administered will be calculated based on the patient's body weight determined within 24 hours of each infusion. The calculated amount of AK002 ([redacted]) based on body weight will be diluted with 0.9% NaCl for IV injection. Final combined volume of each IV bag of AK002 + 0.9% NaCl will be 120 mL. **Note**: Exactly 100 mL of the calculated dose of AK002 will be administered to each patient. The extra 20 mL is to be used to prime the IV infusion line during the preparation of the IV line at the bed side. It is recommended that each dose of 120 mL is prepared in an empty medication delivery bag. The doses for the extension study are outlined in Appendix 2.
Centers/Countries	Approximately 4 study centers in the USA and Germany. Only the sites in Germany will participate in the extension study.
Number of Subjects	N (total) = Approximately 48 subjects with chronic urticaria This will include the following cohorts: • Approximately 12 subjects with Cholinergic urticaria (CholU) • Approximately 12 subjects with Urticaria factitia (UF) • Approximately 12 XOLAIR® (omalizumab) naïve subjects with Chronic spontaneous urticaria (CSU) • Approximately 12 subjects with Chronic spontaneous urticaria (CSU) who did not achieve an adequate response on XOLAIR® (omalizumab) in the opinion of the Investigator The extended dosing will be applicable only to the subjects in the CholU, UF, and CSU-XOLAIR® (omalizumab) failure cohorts.
Rationale for Sample Size	The planned sample size of approximately 48 subjects is based on common practice in early phase, proof-of-concept studies.
Duration of Patient Participation and Duration of Study	The total study duration for each patient will be approximately 32 weeks. This includes: • A screening period of 4 weeks prior to study drug administration • Administration of study drug at Day 1, Day 29, Day 57, Day 85, Day 113, and Day 141 • Follow-up through Day 197 (8 weeks post last dose)

Duration of Patient Participation and Study cont.	Subjects who elect to receive optional extended dosing with up to 12 additional doses of AK002 will participate for up to an additional 12 months (see Appendix 2).
Inclusion Criteria	1) Adults (≥18 and ≤85 years old) 2) Body weight <125 Kg 3) Informed consent signed and dated 4) Able to read, understand, and willing to sign the informed consent form and comply with study procedures 5) Diagnosis of CU for at least 3 months, refractory to antihistamine treatment in single or 4-fold dosage. 6) Willing, committed, and able to return for all clinic visits and complete all study-related procedures, including willingness to have IV infusion of study drug administered by a qualified person 7) Females of childbearing potential must have a negative pregnancy test at Baseline. Female subjects must be willing to use highly effective contraception (Pearl-4 Index <1) or abstain from sexual activity from Screening until the end of the study, or for 120 days following the last dose of study drug, whichever is longer. A woman will be considered not of childbearing potential if she is post-menopausal for greater than two years (FSH >40 mL) or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy). Male patients with female partners of childbearing potential must agree to use a highly effective method of contraception from Screening until the end of the study or for 120 days following the last dose of study drug, whichever is longer. All fertile men with female partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation. 8) No participation in other clinical trials 4 weeks before participation in this study 9) Uncontrolled CU (UCT <12) at the time of enrollment 10) For extended dosing, 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 post-week 22 (Day 155) and by week 44 (Day 309) i.e., within 6 months from last dose
Exclusion Criteria	1) Acute urticaria 2) Concurrent/ongoing treatment with immunosuppressives (e.g., cyclosporine, methotrexate, dapsone, or others) within 4 weeks or 5 half-lives prior to Baseline, whichever is longer

Exclusion Criteria cont.	3) Significant medical condition rendering the patient immunocompromised or not suitable for a clinical trial 4) Significant concomitant illness that would adversely affect the subject's participation or evaluation in this study 5) History of malignancies within five years prior to screening other than a successfully treated non-metastatic cutaneous, basal, or squamous cell carcinoma and/or in situ cancer 6) Presence of clinically significant laboratory abnormalities 7) Lactating women or pregnant women 8) Substance abuse (drug or alcohol) or any other factor (e.g., serious psychiatric condition) within the last 5 years that could limit the subject's ability to comply with study procedures 9) Subjects who are detained officially or legally to an official institute or those that have been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities will be excluded from the study 10) Use of omalizumab within the last 2 months 11) Receipt of intravenous IgG therapy 30 days prior to Baseline 12) Plasmapheresis 30 days prior to Baseline 13) Use (daily or every other day) of Doxepin 14 days prior to Baseline 14) Receipt of inactive vaccination or live attenuated vaccine 30 days prior to Baseline 15) Use of H2-antihistamines 7 days before Baseline 16) Intake of leukotriene antagonists within 7 days prior to enrollment 17) Intake of systemic corticosteroids (e.g., oral or depot) within 14 days prior to enrollment 18) Positive screening for ova and parasite test at Baseline 19) Treatment of helminthic parasite within 6 months of screening 20) Positive HIV serology at screening 21) Positive Hepatitis serology at baseline, except for vaccinated patients or patients with past but resolved hepatitis at screening 22) Donation or loss of >500 mL of blood within 56 days prior to administration of study drug or donation of plasma within 7 days prior to administration of drug 23) Known hypersensitivity to any ingredients of AK002 or drugs related to AK002 (e.g., monoclonal antibodies, polyclonal gamma globulin)

Concomitant Medications	Second-generation H1-antihistamines as concomitant medication once daily and up to 4 times daily on demand (drug intake to be documented in the patient diary).
Safety Evaluations	Safety and tolerability will be assessed throughout the study by monitoring and evaluating adverse events (AEs), including any complications resulting from the IV infusion. All treatment-emergent adverse events (TEAEs) will be collected from the start of study drug administration through 8 weeks after last dose received or Early Termination (ET). Severity will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. All AEs will be assigned a severity grade and relationship to study drug. Additional safety evaluations include clinical laboratory tests, including anti-drug antibody to AK002, complete blood counts, chemistries, and urinalyses, ECGs; and vital signs.
Statistical Methodology	All subjects who received a dose of study drug will be included in the analysis. All safety data will be listed. Where appropriate, summary statistics will be provided (number of non-missing values, mean, median, standard deviation, minimum, and maximum for continuous variables, and number and percentage for categorical variables) for all measures, including demographic and baseline values, clinical scores and safety endpoints.
Rationale for Amendment 4.1	The following modifications have been incorporated into Amendment 4.1 of the protocol. • Procedures that allow subjects in the CholU, UF, and CSU-XOLAIR® (omalizumab) failure cohorts who received all 6 infusions of AK002, were followed through Day 155, and demonstrated severe symptoms of urticaria following discontinuation of treatment, to be offered the option to receive extended dosing with up to 12 additional doses of AK002. Offering extended dosing allows subjects with no other treatment options continued access to AK002 and the benefit obtained during the initial 6 infusions. It also allows for collection of longer-term efficacy, safety, and tolerability data of AK002. • PK will be analyzed retroactively using backup blood samples.

2. Background

2.1 Chronic Urticaria

Chronic urticaria (CU) is a skin condition which is characterized by transient pruritic wheal and flare type skin reactions and, in some patients, the occurrence of angioedema. In Europe, more than 5 million patients are thought to suffer from persisting urticarial symptoms (Maurer, 2011), which either occurs spontaneously (i.e., spontaneous urticaria), or can be induced as a result of environmental physical stimuli such as pressure, ultraviolet irradiation, heat or cold (physical urticaria), or by other means (Metz, 2012). Patients with CU are often severely impaired in their quality of life (Mlynek, 2009), with negative effects on sleep, daily activities, school/work life, and social interactions. The current guidelines of the European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA^2LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) state that the aim of treatment for all types of urticaria is to achieve complete symptom relief (Zuberbier, 2014). However, most patients with chronic spontaneous urticaria (CSU) and all patients with inducible urticaria require symptomatic treatment for effective symptom control. Figure 1 shows the classification of chronic urticaria.

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

* Also called *urticaria factitia*, dermographic urticaria
† Also called cold contact urticaria
‡ Also called pressure urticaria
§ Also called heat contact urticaria

(Zuberbier, 2014)

Figure 1 Classification of Chronic Urticaria

2.2 Cholinergic Urticaria

Cholinergic urticaria (CholU) is a form of inducible urticaria (Zuberbier, 1994; Godse, 2013) that is defined by itching and whealing following the induction of sweating, either actively (e.g., exercise) or passively (e.g., hot bath). CholU must be differentiated from exercise-induced urticaria/anaphylaxis, which is induced by exercise but not passive warming and is more often associated with systemic symptoms. Figure 2 shows a CholU patient after a provocation test.

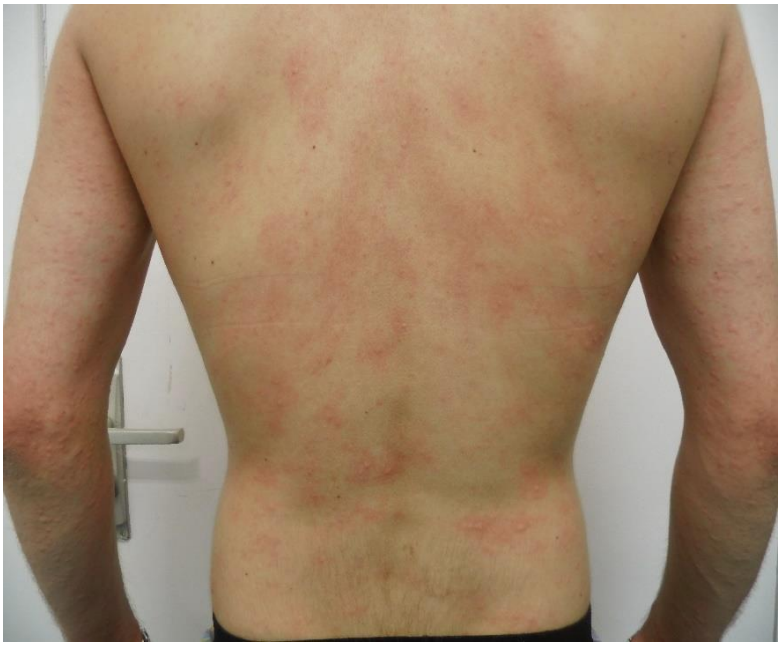
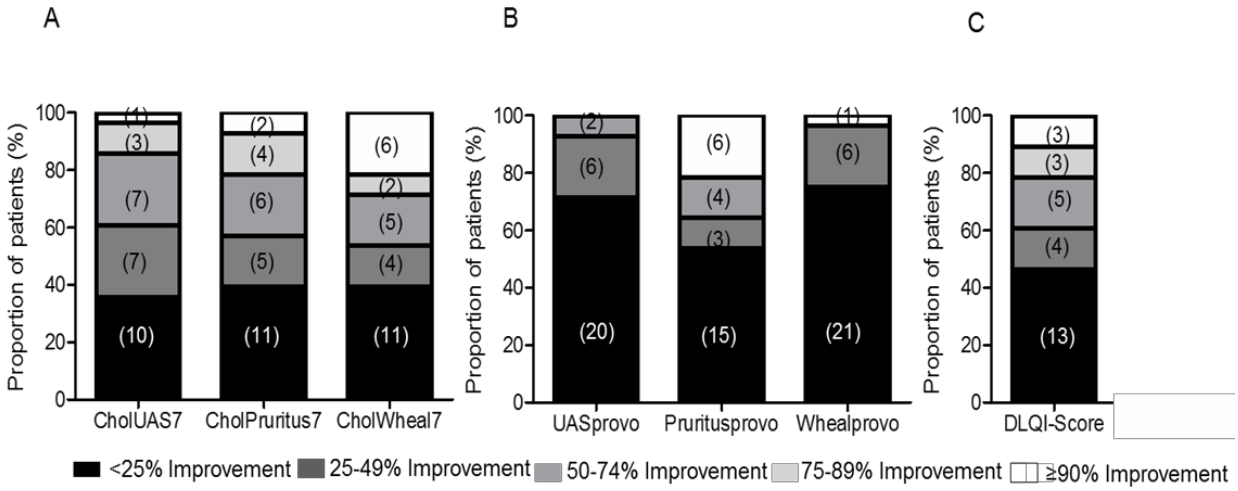


Figure 2 CholU Patient after Provocation Test

CholU is a disorder of young adults and has a high prevalence in this age group (up to 20%) (Zuberbier, 1994). CholU patients typically develop itchy pinpoint sized short-lived wheals with large flare reactions commonly localized to the limbs and the trunk a few minutes after exercise or passive warming. In some patients, emotional stress, or hot and spicy food or beverages can also elicit symptoms. Usually, skin lesions last for 15 to 60 minutes. There is a clear association with atopy (Zuberbier, 1994; Altrichter, 2016) and bronchial hyperresponsiveness (Petalas, 2009) in CholU patients.

Several recent studies indicate that CholU can be due to an allergy to components of human sweat. Some CholU patients show immediate-type hypersensitivity reactions to their own diluted sweat after intradermal injections, and basophils from these patients react to autologous sweat and release high amounts of histamine in vitro (Petalas, 2009; Takahagi, 2009). In addition, CholU patients, but not healthy controls, reportedly express IgE to sweat antigens. Very recently, a new allergen component from a fungus was identified in human sweat (Hiragun, 2013).

The first line treatment options in CholU are avoidance of eliciting triggers and treatment with non-sedating H1-antihistamines. However, many of these patients are not sufficiently treated by antihistamines (Koch, 2016) (Figure 3) and these patients often suffer from the symptoms of CholU and are impaired in their quality of life.



(Koch, 2016)

Figure 3 Antihistamine Updosing only moderately improves Symptoms and Quality of Life in CholU Patients

2.3 Urticaria Factitia

Urticaria factitia (UF; also known as dermographic urticaria and symptomatic dermographism) is a chronic disease characterized by whealing and itching following a minor stroking pressure, rubbing, or scratching of the skin.

In all patients with a history of wheals after stroking of the skin, a provocation test should be performed. This can be done by stroking of the skin lightly with a smooth blunt object (e.g. the tip of a closed ball point pen or a wooden spatula) or a purpose-built instrument, known as a dermographometer. For the diagnosis of symptomatic dermographism, the smooth blunt object should be held perpendicular to the skin and should be used to apply a light stroking pressure to the skin of the upper back or volar forearm. The reaction is considered positive in patients who show a wheal response and report pruritus at the site of provocation (Figure 4).

Patients with a positive test reaction should be evaluated for individual pressure thresholds. For this purpose, a provocation device (FricTest®) has been developed that allows for reproducible and standardized threshold testing. Threshold testing enables physicians to assess disease severity and treatment response more precisely.

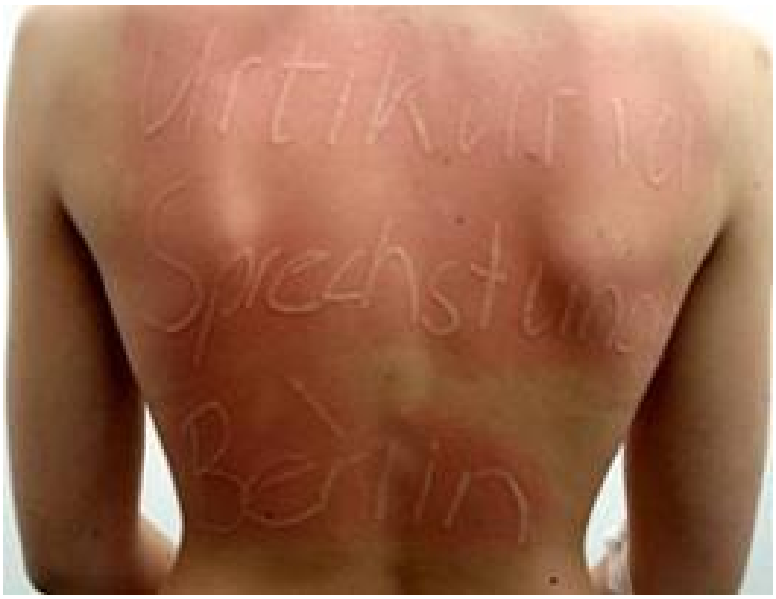


Figure 4 Patient with Urticaria Factitia: Wheal and Flare Development 10–15 minutes after Stroking of the Skin

The majority of patients with urticaria factitia benefit from treatment with non-sedating antihistamines. Some patients, however, do not achieve adequate symptom control even with up-dosing of antihistamines (Borzova, 2008) and may suffer from substantial quality of life impairment (Wallengren, 2007). Since even very minor stroking of the skin can lead to the development of wheals and severe itching, these patients are limited in their choice of clothing and are impaired in their social interactions and partnerships.

2.4 Chronic Spontaneous Urticaria

Chronic spontaneous urticaria (CSU), formerly known by the terms chronic idiopathic urticaria and chronic urticaria (CU), is one of the most frequent skin diseases. In CSU itchy, wheal-and-flare-type skin reactions spontaneously appear on the skin at any time of the day or night (Figure 5). These symptoms can also occur several times per day and each skin eruption can persist up to 24 hours. At any time, 0.5–1% of the population suffers from the disease (Maurer, 2011). Although all age groups can be affected, the peak incidence is seen between 20 and 40 years of age. The duration of the disease is generally several years but is likely to be longer in more severe cases, cases with concurrent angioedema, in combination with physical urticaria or with a positive autologous serum skin test (autoreactivity). CSU has detrimental effects on quality of life, with sleep deprivation and psychiatric comorbidity being frequent. It also has a large impact on society in terms of direct and indirect health care costs, as well as reduced performance at work and in private life (Maurer, 2011). In many patients, an underlying cause of CSU cannot be identified making a causal and/or curative treatment difficult.

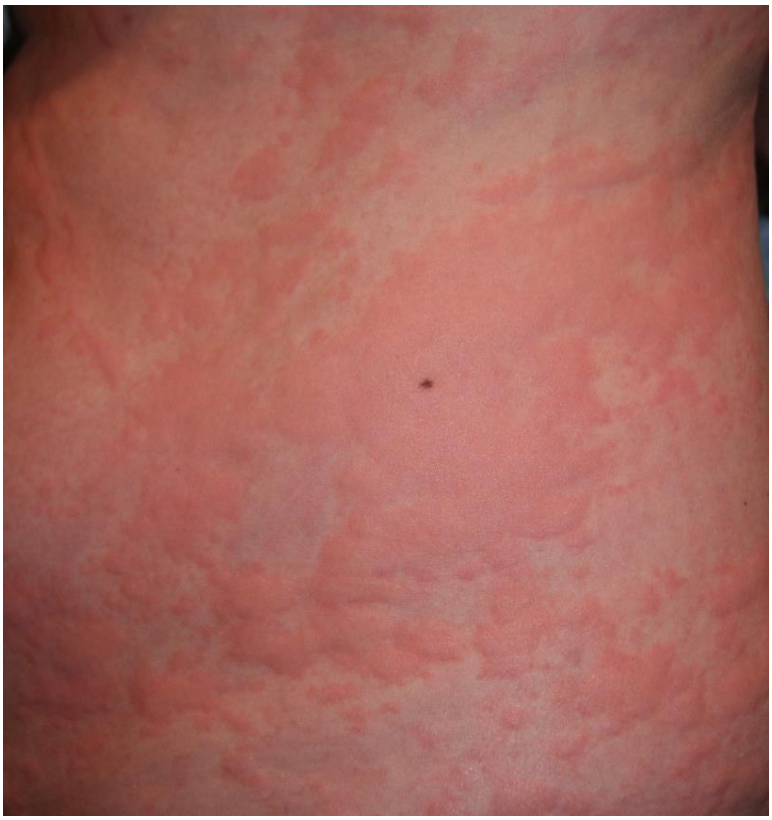


Figure 5 Patient with CSU: Spontaneous Wheal, Flare, and Itch

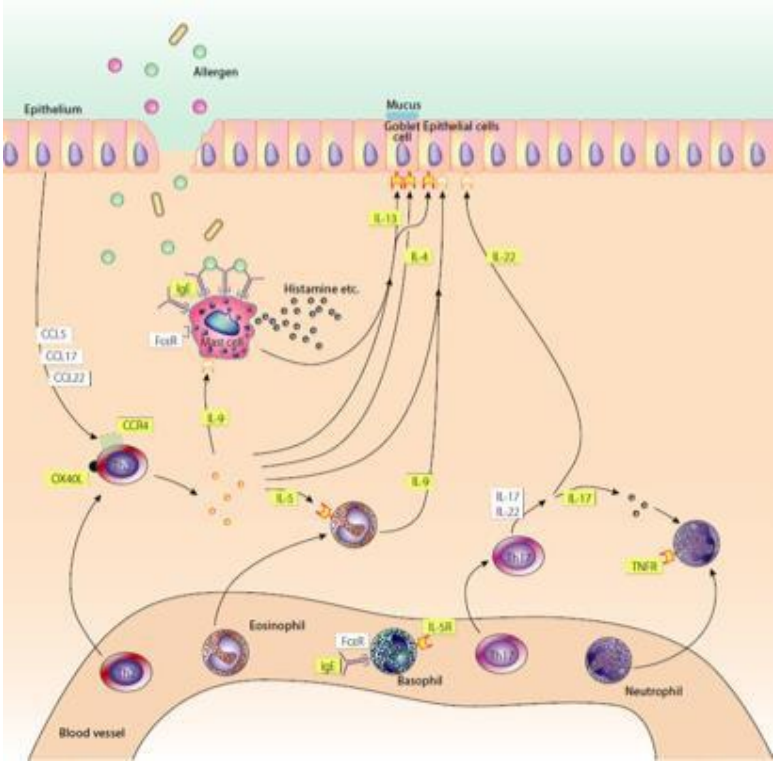
2.5 Current Therapies for CU

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

In double-blind placebo-controlled studies in selected antihistamine-refractory patients, omalizumab has been shown to be very effective in the treatment of CSU and is recommended as third-line therapy if symptoms persist with four-fold antihistamines. However, some CSU patients continue to have symptoms despite omalizumab treatment or do not respond at all to omalizumab treatment. Furthermore, omalizumab is not licensed for the treatment of chronic inducible urticaria (CINDU). Therefore, there is a significant unmet need for new targeted therapeutic options for patients with CSU and CINDU.

2.6 Siglec-8

Siglec-8 is a member of the CD33-related family of Siglecs (sialic acid immunoglobulin-like lectins) with a restricted tissue distribution, expressed selectively on the surface of mature eosinophils, mast cells, and at lower levels on basophils, but not in early precursors of these cell populations or other blood cells (Figure 6). Siglec-8 is expressed at equivalent levels on mast cells obtained from peripheral blood and from bone marrow of patients with systemic mastocytosis and on resting and activated eosinophils obtained from peripheral blood and from several tissues in patients with a variety of atopic disorders, including nasal polyps and asthma (Falahati, 2015; Nutku, 2005; Nutku-Bilir, 2008). Engaging Siglec-8 results in the inhibition of release of mediators from mast cells without affecting their survival. Therefore, Siglec-8 is a novel and promising target for the treatment of mast cell-mediated diseases, especially CU (James, 2012).



(Boyman, 2015)

Figure 6 Potential Pharmacological Targets in T Helper Cell-Driven Diseases

Antibody engagement of Siglec-8 on mast cells and eosinophils can result in inhibition of mediator release from mast cells and eosinophils. AK002 is a non-fucosylated IgG1 antibody with antibody-dependent cellular cytotoxicity (ADCC) activity against Siglec-8 expressing target cells. In the presence of effector cells of the immune system, such as natural killer cells, the antibody also shows eosinophil and mast-cell depleting activity. By reducing the number of

blood and tissue eosinophils and reducing the number of tissue mast cells and/or blocking degranulation and induction of mast-cell derived mediators, AK002 may be useful in the treatment of patients with chronic urticaria.

2.7 Overview of Animal Studies with AK002

To evaluate the in vivo activity of anti-Siglec-8 antibodies in an immunocompetent rodent model, a transgenic mouse strain has been developed that selectively expresses human Siglec-8 on the surface of mouse mast cells (MCs), eosinophils, and basophils. In single- and repeat-dose studies in Siglec-8 transgenic mice, AK002 demonstrated selective depletion of peritoneal MCs and circulating and tissue (spleen) eosinophils and basophils. AK002 was well tolerated in single and repeat-dose pharmacology studies.

In 2 Good Laboratory Practice (GLP) toxicity studies, Siglec-8 transgenic mice received weekly intravenous (IV) doses of AK002 weekly for 4 weeks (5 total doses) or 6 months at 2 dose levels, 50 mg/kg and 100 mg/kg. The high dose, 100 mg/kg, was selected to represent a dose 10-fold higher than the highest proposed clinical dose, 10 mg/kg. Consistent with its mechanism of action, AK002 decreased eosinophils at both doses. There were no adverse AK002-related effects on survival, body weights, clinical observations, clinical pathology, or anatomic pathology at either dose. The no-observed-adverse-effect level (NOAEL) following repeat IV administration of AK002 to transgenic mice was 100 mg/kg.

2.8 Overview of Prior Clinical Studies with AK002

AK002 has been studied in two Phase 1 studies: one ongoing clinical trial in Germany (AK002-001) in patients with indolent systemic mastocytosis (ISM) and one completed Phase 1 clinical trial in healthy volunteers in Australia (AK002-002).

- Study AK002-001, A Phase 1, Single Ascending Dose and Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AK002 in Patients with Indolent Systemic Mastocytosis, is in progress in patients with ISM. Up to 30 patients will receive AK002: single IV infusion in 6 single-patient cohorts at 0.0003 mg/kg, 0.001 mg/kg, 0.003 mg/kg, 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg; single IV infusion in two 3-patient cohorts at 0.3 mg/kg and 1 mg/kg; and up to 6 patients in a cohort with up to 6 infusions of 1 mg/kg every 28 days. In addition, two subjects have received a dosing regimen of 1 mg/kg, followed by 3 mg/kg for another 2 infusions. In the single-dose cohorts, all of which have been completed, AK002 has been generally well tolerated. Mild infusion-relate reactions (IRRs) (nausea, vomiting, abdominal pain, flushing, dyspnea, headache, or hypertension) have been observed. Temporal interruption of the AK002 infusion and minimal intervention have resulted in prompt resolution of symptoms and ability to

complete the infusion without further complications. In patients with ISM receiving doses of 0.1–3 mg/kg, objective measures of skin reactivity on stimulation (Darier's sign) have improved, and [redacted] patients have reported substantial improvements in symptoms including resolution of diarrhea, reductions in pruritus, skin flushing or urticarial rashes, as well as qualitative improvements in abdominal pain and fatigue.

- Study AK002-002, A Phase 1, Double-Blind, Placebo-Controlled, Single Ascending Dose and Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AK002 in Healthy Participants, compared AK002 with placebo in healthy volunteers, has completed enrollment and follow-up. In total, 51 subjects were enrolled: [redacted] AK002-treated subjects and [redacted] placebo-treated subjects. Subjects received a single IV infusion in one 4-subject cohort at 0.001 mg/kg (all subjects received AK002), single IV infusion in six 6-subject cohorts at 0.003 mg/kg, 0.01 mg/kg, 0.03 mg/kg, and 0.1 mg/kg; 0.3 mg/kg and 1 mg/kg (4 subjects received AK002 and 2 subjects received placebo in each cohort); 8 subjects in a cohort with 2 infusions of 0.3 mg/kg every 28 days (6 subjects received AK002 and 2 subjects received placebo); and 3 subjects in a cohort with 2 infusions of 1 mg/kg every 28 days (2 subjects received AK002 and 1 subject received placebo). Among the 51 enrolled subjects, only 1 subject experienced a delayed IRR that was considered a serious adverse event (SAE): a 24-year old Caucasian woman developed nausea, emesis, chills, and rigors and felt pre-syncopal 3 hours after receiving a 1 mg/kg dose of AK002. She received promethazine, normal saline, hydrocortisone, and metoclopramide and was noted to have a decrease in blood pressure. She was treated with 0.3 mg adrenaline IM, and blood pressure quickly stabilized. No further urgent treatment was required, and she recuperated without any sequelae. Mild IRRs comprising nasal congestion, headache, nausea, and throat and chest tightness have been observed. When reactions did occur during the infusion, temporal interruption of the AK002 infusion and minimal intervention resulted in prompt resolution of symptoms and ability to tolerate the infusion without further complications. Of note, in the multiple-dose cohort, subjects were able to tolerate the second study drug infusion better than the first study drug infusion. This observation is consistent with rates of IRRs observed with other monoclonal antibodies with ADCC activity.

In both Phase 1 studies, AK002 at all doses was active at its target and caused rapid deletion of eosinophils, consistent with its mechanism of action. The duration of eosinophil depletion corresponded with the detection of AK002 in the blood.

3. Study Design

This is an exploratory, proof-of-concept, open-label pilot study to assess the effects and safety of AK002 in subjects with CU refractory to standard treatment (single-dose antihistamine treatment).

This design is intended to assess the effects and safety of AK002 in subjects with CU refractory to standard treatment. Following this study, if this indication is pursued, a randomized double-blind placebo-controlled study will be considered.

4. Objectives

4.1 Primary Objective

To assess the efficacy of AK002 on symptoms in subjects with CU (change in urticaria control test; UCT score)

4.2 Secondary Objectives

The effect of AK002 on urticaria symptoms, QOL, provocation testing, and histological criteria

The efficacy, safety and pharmacodynamics of AK002 in CU subjects will be assessed through the following evaluations:

1) Safety and tolerability (adverse events, laboratory safety tests, etc.)
2) Disease activity scores (UAS7, [redacted])
3) [redacted]
4) Number of symptom-free days
5) Use of rescue medication (up to 3 sgAH tablets/day)
6) Effects on [redacted]
7) Number of [redacted]
8) [redacted]
9) Changes in trigger thresholds (in CINDU, including CholU)
10) Rate of [redacted] (UCT, [redacted]
11) Serum levels of potential biomarkers of disease activity and treatment responses
12) Rates of relapse and sustained response (during post-treatment follow-up period)

5. Endpoints

5.1 Primary Endpoint

The primary endpoint is the change in Urticaria Control Test (UCT), a score for symptom control in chronic urticaria, from Day 1 (baseline) to Week 22 in CU subjects after treatment with AK002. At Baseline, a 4-week recall will be recorded, prior to first study drug administration. A change of the UCT score of 3 or more points is regarded as clinically relevant (minimal clinically important difference [MCID]).

5.2 Other Endpoints

1) Safety of subjects treated with AK002: This includes physical examination, routine safety laboratory assessments, vital signs, electrocardiogram (ECG), urine safety, and adverse event reporting (Visits 2–10)
2) Change in disease activity as assessed by UAS7 and/or [redacted] (from Baseline to Visits 3, 5, 8, and 10)
3) Change in number of symptom-free days per week (patient diary-based CSU score; wheals, flares, itch, avoidance behavior) from Baseline to Visits 3, 5, 8, and 10
4) Change in [redacted] assessed by [redacted] from Baseline to Visits 3, 5, 8, and 10
5) Change in number of intake of rescue medication from Baseline to Visits 3, 5, 8, and 10
6) In case of [redacted], change in [redacted] from Visit 2 to Visit 3, 5, 8, and 10, as assessed by [redacted]
7) Change in number of [redacted] from Baseline to Visits 3, 5, 8, and 10
8) Change in [redacted] from Baseline to Visits 3, 5, 8, and 10
9) Changes in trigger threshold from Baseline to Visits 2, 3, 5, 8, and 10, as assessed by Pulse Controlled Ergometry Test (PCE) and FricTest®, as applicable
10) Rates of complete response, partial response, and non-response based on UCT, [redacted], trigger thresholds (where applicable), and QoL from Baseline to Visits 3, 5, 8, and 10
11) Serum levels at baseline and change from Baseline to Visits 3, 5, 8, and 10 of serum levels of potential biomarkers in AK002-treated subjects (e.g., tryptase, eosinophils, total IgE, basophils, eosinophil cationic protein)
12) Rates of AK002-treated subjects with relapse, rebound, sustained treatment effects at Visit 7

6. Investigational Plan

6.1 Study Design

The study comprises a screening period of 4 weeks, with daily oral intake of standard-dose (once daily) second-generation 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. Subjects will be followed for an additional 8 weeks, and at Weeks 22, 24, and 28 the primary and secondary objectives will be evaluated.

It is expected that approximately 48 subjects will be enrolled and assigned to 3 cohorts:

- Approximately 12 subjects with Cholinergic Urticaria (CholU)
- Approximately 12 subjects with Urticaria Factitia (UF)
- Approximately 12 XOLAIR® (omalizumab) naïve subjects with Chronic spontaneous urticaria (CSU)
- Approximately 12 subjects with Chronic spontaneous urticaria (CSU) who did not achieve an adequate response to XOLAIR® (omalizumab) in the opinion of the Investigator

The open-label design facilitates the assessment of efficacy, as well as safety in the cohort. Table 1 shows the study outline and Table 3 shows the schedule of assessments.

Table 1 Study Outline

Screening	Treatment						Follow-up		
	0.3 mg/kg	1 mg/kg	1 mg/kg	3 mg/kg*	3 mg/kg*	3 mg/kg*	1	2	3
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Week -4	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 22	Week 24	Week 28
Day -28	Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 155	Day 169	Day 197

* Increase to 3 mg/kg if UCT score is <12 and/or at the discretion of the Investigator in consultation with the Allakos Medical Monitor. If UCT score is ≥12, and if the Investigator in consultation with the Medical Monitor feels that the patient has experienced adequate symptom improvement, then continue with the 1 mg/kg dose.

6.1.1 Screening Period

At the beginning of the screening period**,** eligible subjects will be asked to sign the informed consent form (ICF) and their current medication will be discussed. During the screening period, subjects will continue with their current antihistamine medication (approved dose). 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. A patient is considered enrolled in the trial when the patient receives their first dose of AK002.

6.1.2 Treatment Period

During the Treatment Period, all eligible subjects will receive AK002 by IV infusion every 28 days. The first dose will be administered at the beginning of the treatment period Day 1 (Visit 2) after baseline measurements. At Day 141 (±2 days) (Visit 7), the final dose of AK002 will be given. Throughout the treatment period, subjects must maintain stable doses of their baseline AH dose and treatment regimen and remain on a stable treatment regimen through the end of the study. Patient's use of rescue medication will be monitored and reviewed throughout the treatment period and if necessary adjusted according to the current urticaria guidelines (Zuberbier, 2014). Subjects are expected to attend all site visits based on the assessment schedule (see Table 3).

6.1.3 Follow-Up Period

After completion of the Treatment Period, all subjects enter an 8-week follow-up period to obtain further information on the impact of AK002 treatment on urticaria activity and relapse of symptoms. No investigational treatment will be given during the post-treatment Follow-up Period; however, subjects are allowed to take their rescue medication. Rescue medication (a non-sedating antihistamine) will be provided and used on an as-needed basis during the post-treatment Follow-up Period.

6.1.4 Extended Dosing (Optional)

Subjects in the CholU, UF, and CSU-XOLAIR® (omalizumab) failure cohorts who received all 6 infusions of AK002, were followed through at least through Day 155, and demonstrated severe recurring symptoms of urticaria following discontinuation of treatment (as defined below) will be eligible to receive extended dosing with up to 12 additional doses of AK002 (see Appendix 2).

To qualify for extended dosing, 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 recorded between Day 155 and Day 309 (i.e., within 6 months from last dose).

6.2 Rationale for the Study Design

This exploratory clinical trial is designed to evaluate the efficacy and safety of AK002 in subjects with chronic urticaria. AK002 is a novel monoclonal antibody that inhibits Siglec-8, expressed on mast cells, eosinophils, and to a lesser degree, on basophils. Considering that CU is

regarded as mast cell-driven disease, it is reasonable to assume that AK002 could be beneficial in CU.

The gold standard treatment of CU comprises administration of antihistamines. In severe cases, antihistamines can be increased up to 4 times the standard dose. But there remains a significant proportion of subjects with CU that is not sufficiently controlled despite high doses of antihistamines, displaying a clear unmet medical need (Koch, 2016). CINDU subjects have no other treatment option. Therefore, there is an unmet need for new targeted therapeutic options for subjects with CSU and CINDU. This study will provide valuable insights into the therapeutic potential of AK002 in improving quality of life in these subjects, in addition to reducing CU symptoms.

This design is intended to assess the effects and safety of AK002 in subjects with CU refractory to standard treatment. Following this study, if this indication is pursued, a randomized double-blind placebo-controlled study will be considered.

6.3 Rationale for the Dose/Regimen, Route of Administration, and Duration of Treatment

6.3.1 Rationale for AK002 Dose and Regimen

The proposed AK002 dose of 0.3 mg/kg administered at Day 1 and increased to 1 mg/kg at Day 29, Day 57, and subsequently to 3 mg/kg on Days 85, 113, and 141 is based on prior experience with AK002 in healthy volunteers and in subjects with ISM. Also, the long-term continuation treatment will provide the option of an additional 12 months of treatment for patients with severe disease at baseline who recorded a complete response while on treatment with AK002 (1 mg/kg or 3 mg/kg) and who developed severe symptoms within 6 months of discontinuing AK002. The continuation protocol will be limited to patients who have no other treatment options, that is CholU, UF, or Xolair failures in patients with CSU.

Subjects with ISM receiving 0.3 mg/kg, 1 mg/kg, and 3 mg/kg AK002 have reported improvement of their clinical symptoms in a dose-dependent fashion. For example, some ISM patients who showed some response to 1 mg/kg, showed improved symptom control when the dose was increased to 3 mg/kg. In general, AK002 was well tolerated in these subjects. A dose of 0.3 mg/kg resulted in suppression of eosinophils for approximately 1 month, which would justify a monthly dosing regimen. In addition, a starting dose of 0.3 mg/kg has demonstrated an adequate safety and tolerability profile in previous and current clinical trials.

6.3.2 Rationale for Concomitant Antihistamine Dose and Regimen

The target population for this study comprises CU subjects who remain symptomatic despite treatment with AH therapy alone (at approved doses). The updated International Guideline on definition, classification, diagnosis, and management of urticaria (Zuberbier, 2014), evidence-based recommendations by an international expert team, has led to a treatment algorithm that recommends as Step 1 and Step 2 the use of non-sedating AHs at approved, or increased doses (up to 4-fold), respectively. As Step 3, the addition of omalizumab, cyclosporin A, or montelukast (LTRA) is recommended. None of the therapeutic recommendations of Step 2–3 are currently licensed for subjects with CINDU, including CholU and UF; therefore, to reflect the most current treatment algorithm for CINDU subjects, this study allows use of AH (at approved doses) as background medication.

6.4 Risks and Benefits

The inclusion and exclusion criteria are selected to enroll subjects with CU most likely to benefit from participating in the study. The overall risk will be minimized by compliance with the inclusion/exclusion criteria, close clinical monitoring including the use of a diary to monitor symptoms, and the use of rescue medication. See the Investigator Brochure for the complete safety summary of AK002.

The long-term continuation treatment will provide the option of an additional 12 months of treatment for patients with severe disease at baseline who recorded a complete response while on treatment with AK002 (1 mg/kg or 3 mg/kg) and who developed severe symptoms within 6 months of discontinuing AK002. The continuation protocol will be limited to patients who have no other treatment options, that is CholU, UF, or Xolair failures in patients with CSU.

The Investigator will provide the patient with written instructions to contact them if symptoms of CU worsen. Investigators will be instructed on acceptable treatments for worsening CU, which will allow subjects to continue on the study. The clinical benefits and safety profile of AK002 in subjects with CU has not yet been established. The risk for subjects participating in this study includes the potential for known safety issues, such as hypersensitivity reactions including anaphylaxis (Appendix 1), as well as for any unknown safety effects that could occur.

7. Population

The study population will be comprised of approximately 48 adult subjects (≥18 and ≤85 years old) with the diagnosis of CU. Approximately 12 subjects of each subgroup of CU (CholU, UF, CSU-XOLAIR® (omalizumab) naïve, CSU-XOLAIR® (omalizumab) failures) will be recruited. Subjects with acute urticaria will be excluded.

Approximately 48 subjects enrolled at approximately 4 study centers in the USA and Germany are expected to participate in the study.

7.1 Rationale for the Number of Subjects

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

7.2 Inclusion/Exclusion Criteria

The Investigator must ensure that all subjects meet the following inclusion criteria and none of the exclusion criteria.

7.2.1 Inclusion Criteria

1) Adults (≥18 and ≤85 years old)

2) Body weight <125 Kg

3) Informed consent signed and dated

4) Able to read, understand, and willing to sign the informed consent form and comply with study procedures

5) Diagnosis of CU for at least three months, refractory to antihistamine treatment in single or 4-fold dosage

6) Willing, committed, and able to return for all clinic visits and complete all study-related procedures, including willingness to have IV infusion of study drug administered by a qualified person

7) Females of childbearing potential must have a negative pregnancy test at Baseline. Female subjects must be willing to use highly effective contraception (Pearl-4 Index <1) or abstain from sexual activity from Screening until the end of the study, or for 120 days following the last dose of study drug, whichever is longer. A woman will be considered not of childbearing potential if she is post-menopausal for greater than two years (FSH >40 mL) or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy).

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

8) No participation in other clinical trials 4 weeks before participation in this study

9) Uncontrolled CU (UCT <12) at the time of enrollment

10) For extended dosing, 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).

7.2.2 Exclusion Criteria

1) Acute urticaria

2) Concurrent/ongoing treatment with immunosuppressives (e.g., cyclosporine, methotrexate, dapsone, or others) within 4 weeks or 5 half-lives prior to Baseline, whichever is longer

3) Significant medical condition rendering the patient immunocompromised or not suitable for a clinical trial

4) Significant concomitant illness that would adversely affect the subject's participation or evaluation in this study

5) History of malignancies within five years prior to screening other than a successfully treated non-metastatic cutaneous, basal, or squamous cell carcinoma and/or in situ cancer

6) Presence of clinically significant laboratory abnormalities

7) Lactating women or pregnant women

8) Substance abuse (drug or alcohol) or any other factor (e.g., serious psychiatric condition) within the last 5 years that could limit the subject's ability to comply with study procedures

9) Subjects who are detained officially or legally to an official institute or those that have been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities will be excluded

10) Use of omalizumab within the last 2 months

11) Receipt of intravenous IgG therapy 30 days prior to Baseline

12) Plasmapheresis 30 days prior to Baseline

13) Use (daily or every other day) of Doxepin 14 days prior to Baseline

14) Receipt of inactive vaccination or live attenuated vaccine 30 days prior to Baseline

15) Use of H2-antihistamines 7 days before Baseline

16) Intake of leukotriene antagonists within 7 days prior to enrollment

17) Intake of systemic corticosteroids (e.g., oral or depot) within 14 days prior to enrollment

18) Positive screening for ova and parasite test at Baseline

19) Treatment of helminthic parasite within 6 months of screening

20) Positive HIV serology at screening

21) Positive Hepatitis serology at baseline, except for vaccinated patients or patients with past but resolved hepatitis at screening

22) Donation or loss of >500 mL of blood within 56 days prior to administration of study drug or donation of plasma within 7 days prior to administration of drug

23) Known hypersensitivity to any ingredients of AK002 or drugs related to AK002 (e.g., monoclonal antibodies, polyclonal gammaglobulin)

8. Study Treatment

8.1 Investigational Treatment

AK002 will be administered as an intravenous (IV) infusion at a dose of 0.3 mg/kg given over a period of approximately 4 hours on Study Day 1. If well tolerated, dose will be increased to 1 mg/kg, given over a period of approximately 4 hours on study Day 29 and Day 57 (±2 days). Dose will be increased to 3 mg/kg on Days 85, 113, and 141 (±2 days) if the UCT score is <12 and/ or at the discretion of the Investigator in consultation with the Allakos Medical Monitor. If the UCT score ≥12, and if the Investigator in consultation with the medical monitor feels that the patient has received adequate symptom improvement, patient will remain at the 1 mg/kg dose. All doses will be given over a period of approximately 4 hours. The duration of infusion and the rate at which the infusion is given may be adjusted based on Investigator discretion.

The amount of AK002 to be administered will be calculated based on the patient's body weight determined within 24 hours of each infusion.

8.2 Concomitant Treatment

One hour prior to dosing with AK002, subjects will receive pre-treatment oral doses of acetaminophen/paracetamol (1000 mg) and cetirizine (10 mg) for doses 1 and 2. Any premedication for subsequent doses will be based on the Investigator's discretion.

Subjects will be treated with a standard dose of second-generation AH (once per day) or up to a 4-fold dose of second-generation AH (standard of care) with dose and regimen established during Screening. In the event of symptom resolution during the study, the dose and schedule of AH treatment established during screening must be continued throughout the study.

8.3 Treating the Patient

8.3.1 Patient Numbering

Each patient will be assigned a Patient ID Number (PID) by the site after the patient provides written informed consent. Each patient is uniquely identified in the study by a combination of the study number, site number and the patient's disease code.

- The first 3 digits will designate the study number, as assigned by Allakos (206 for this study).
- The next 3 digits will designate the site number, as assigned by Allakos.
- The last 3 digits will designate the disease code and order of consent at the site.
  - Disease codes are as follows: 1 = CholU, 2 = UF, 3 = CSU (Xolair Naïve), and 4 = CSU (Xolair Failure)
  - The first patient consented at each site will be assigned their disease code + "01", and subsequent subjects will be assigned consecutive numbers based on consent order at the site (e.g., the second patient consented at the site will be assigned their disease code + "02", and the third patient consented at the site will be assigned their disease code + "03", etc.)

  Example: For example, Site 003 consented 4 patients. The first patient has CSU (Xolair Naïve), the second patient has UF, the third patient has CholU, and the fourth patient has CSU (Xolair Failure). The first patient will be assigned PID 206-003-301, the second patient assigned PID 206-003-202, the third patient assigned PID 206-003-103, and the fourth patient assigned PID 206-003-404.

Once assigned to a patient, a PID number will not be reused. The patient will maintain the same PID number throughout the entire study except if the patient fails the first screening. If a patient signs the ICF but does not meet the inclusion/exclusion criteria, the patient will be considered a screen failure. The patient can be re-screened one additional time during the clinical trial.

However, if this occurs the site will assign the patient a new PID at the subsequent screening visit. If the ICF has been signed within 30 days and there are no new revisions, a new ICF is not necessary.

8.3.2 Formulation of AK002

AK002 is a humanized non-fucosylated IgG1 monoclonal antibody directed against Siglec-8. AK002 Drug Product is supplied as a sterile liquid in a single-use 10R glass vial with a fill volume of not less than 10 mL. The AK002 formulation is [redacted] (use [redacted] for dose prep) AK002 in [redacted] pH 6.0, in sterile water for injection.

Allakos, Inc. will supply the investigational site with AK002. AK002 must not be shaken or frozen. AK002 will be stored by the study site at 2–8ºC under lock, pending drug preparation. Access will be restricted to designated study pharmacy staff. All clinical supplies will be temperature controlled and monitored. If the temperature of study drug storage in the clinic/pharmacy exceeds or falls below this range, this will be reported to the Principal Investigator and captured as a deviation.

The NaCl 0.9% for IV injection is commercially available and will be ordered as needed. The NaCl 0.9% should be stored at room temperature.

Study drug will be administered by IV infusion using an infusion pump. Dose preparation and administration details are included in the study Pharmacy Manual.

8.3.3 Supply of AK002 to the Investigational Site

The Sponsor (or designee) will ship study drug to the investigational sites. The initial study drug shipment will be shipped after site activation (i.e., after all required regulatory documentation has been received by the Sponsor and a contract has been executed). Subsequent study drug shipments will be made by the Sponsor or designee.

Each vial will be labeled with the required investigational use statement, lot number, and directions for storage.

8.3.4 Preparation of Study Drug

Please refer to the Pharmacy Manual for additional details regarding study drug preparation.

The amount of AK002 to be administered will be calculated based on the patient's body weight determined within 24 hours of each infusion.

The calculated amount of study drug based on body weight will be diluted with 0.9% NaCl for IV injection.

The final combined volume of the IV bag of study drug + 0.9% NaCl will be **120** mL.

Note: Exactly **100 mL** of the calculated dose of study drug will be administered to the patient. The extra 20 mL is to be used to prime the IV infusion line during the preparation of the IV line at the bed side.

It is recommended that each dose of 120 mL is prepared in an empty medication delivery bag.

For all 6 doses (0.3 mg/kg on Day 1, 1 mg/kg on Day 29 and Day 57, and 3 mg/kg on Day 85, Day 113, and Day 141), 100 mL dose of study drug will be infused over approximately 4 hours.

After each dose, the patient will be monitored for at least 4 hours after IV administration. At the discretion of the PI, monitoring may be extended for an additional 24 hours.

Detailed instructions for preparing the drug are in the Pharmacy Manual.

8.3.5 AK002 Administration

Premedication with oral doses of acetaminophen/paracetamol (1000 mg) and cetirizine (10 mg) will be given 1 hour prior to the infusion for doses 1 and 2. Any premedication for subsequent doses will be based on the Investigator's discretion. AK002 will be infused through a peripheral vein IV set. The IV line will be kept open before and after the infusion with sufficient quantities of 0.9% NaCl to assure patency.

Based on the patient's weight, the designated clinical staff will prepare the appropriate dilution of AK002 at 0.3 mg/kg (for Day 1), 1 mg/kg (for Day 29 and Day 57), and 3 mg/kg (for Day 85, Day 113, and Day 141) for IV administration. Appropriate aseptic technique will be used, and the study drug will be prepared according to the Pharmacy Manual for AK002.

The site's designated clinical staff will keep accurate and current accounting of the preparation and dose calculation of study drug for each patient, with source, quantities of study medication dispensed, used, and returned. All dosage calculations will be documented on the source documents. A study drug receipt, dispensation, and disposition log will be maintained by the pharmacist on the Investigational Drug Accountability Record. A study monitor will verify entries on these documents throughout the course of the study.

Specific instructions on administration are detailed in the Pharmacy Manual. In general, all doses i.e., 0.3 mg/ kg at Day 1, 1 mg/kg at Day 29 and Day 57, and either 1 mg/kg or 3 mg/kg (depending on UCT score) at Day 85, Day 113, and Day 141 will be given as an IV infusion over approximately 4 hours, following an observation period of 4 hours.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the appropriate eCRF.

Subjects in the CholU, UF, and CSU-XOLAIR® (omalizumab) failure cohorts who received all 6 infusions of AK002, were followed through Day 155, and demonstrated severe symptoms of urticaria following discontinuation of treatment will be eligible to receive extended dosing with up to 12 additional doses of AK002 (see Appendix 2).

For extended dosing, 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 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.

8.3.6 Permitted Study Drug Dose Adjustments and Interruptions

AK002 dose adjustments are not permitted. The IV infusion may be interrupted, and/or the rate may be reduced by 50%, if a patient experiences an infusion-related reaction. The time the infusion is initiated/concluded (including any interruptions) will be documented in the eCRF. Infusion interruptions and infusion rate reductions should be documented when reporting any infusion-related reaction AEs. If dose is restarted after an interruption, the infusion must be completed within the 8-hour stability window. Administration will be discontinued if, in the opinion of the Investigator, an interrupted infusion cannot be restarted for safety reasons or if the infusion cannot be completed within the 8-hour stability window.

Administration will also be discontinued in any patient experiencing an SAE during the course of the infusion. A lower infusion rate in new subjects will be considered after assessment of safety results and discussion with the Medical Monitor.

Acetaminophen, antihistamines, and, if needed, a glucocorticoid (e.g., 125 mg methylprednisolone IV) may be administered to the patient if the patient experiences reactions that are considered mild to moderate (e.g., itching or a localized rash) at the Investigator's discretion. If a patient experiences signs or symptoms of anaphylaxis, the patient will be treated with standard of care, such as diphenhydramine, acetaminophen, methylprednisolone, epinephrine, and other supportive measures along with cessation of the infusion. As part of the anaphylaxis assessment, a sample of blood should be obtained for plasma histamine and tryptase level within 1 to 2 hours of the onset of the symptoms.

Any missed or altered study drug administrations must be recorded on the Dosage Administration Record eCRF in order to reconstruct an accurate dosing history for each patient.

8.3.7 AK002 Accountability

The site's designated pharmacist will keep accurate and current accounting of the preparation and dose calculation of study drug for each patient, with source, quantities of study medication dispensed, used, and returned. All dosage calculations will be documented in the source documents. A study drug receipt, dispensing, and disposition log will be maintained by the pharmacist on the Investigational Drug Accountability Record. A study monitor will verify entries on these documents throughout the course of the study.

Used study drug vials must be inspected by the study monitor prior to destruction or return to the study drug vendor.

8.3.8 Measures of Treatment Compliance

AK002 will be administered under supervision of the Principal Investigator or Sub-Investigator. The calendar date and 24-hour clock times when the infusion is initiated and concluded, including any interruptions, will be documented in the eCRF.

8.3.9 Dietary and Lifestyle Restrictions

Subjects will refrain from alcohol and strenuous exercise (e.g., heavy lifting, weight training, aerobics) for at least 24 hours prior to each blood collection for clinical laboratory tests. Subjects will fast for at least 8 hours before blood for clinical laboratory tests is obtained.

8.3.10 Prohibited Treatments

Use of the class of treatments displayed in Table 2 is **NOT** allowed after start of screening (Visit 1). The minimum required period without prohibited treatment before Visit 2 is also listed in Table 2.

Table 2 Prohibited Treatments

Medication	Minimum Required Period without Medications
Omalizumab	within 2 months of Baseline
H2-antihistamines	7 days prior to Baseline
Routine (daily or every other day during 5 or more consecutive days) doses of systemic corticosteroids	14 days prior to Baseline
Routine (daily or every other day during 5 or more consecutive days) doses of systemic hydroxychloroquine	30 days prior to Baseline
Routine (daily or every other day during 5 or more consecutive days) doses of methotrexate, cyclosporine A, cyclophosphamide, tacrolimus and mycophenolate mofetil	4 weeks or 5 half-lives prior to Baseline
Intravenous immunoglobulin G	30 days prior to Baseline
Plasmapheresis	30 days prior to Baseline
Regular (daily or every other day) doxepin (oral)	14 days prior to Baseline
Inactive vaccination	30 days prior to Baseline
Live attenuated vaccine	30 days prior to Baseline
Leukotriene Antagonists	7 days

If the prohibited treatment was used during the study for any indication, the patient must discontinue use of the prohibited treatment if he/she wishes to continue in the study. If the patient received a live virus vaccination during the study, the patient must discontinue study treatment.

The list of prohibited medications is not considered all inclusive. Medication should be assessed for adherence to the indication and other inclusion/exclusion criteria.

The Investigator should instruct the patient to notify the study site about any new medications he/she takes subsequent to receiving the study drug. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered following initial study drug treatment, must be listed on the concomitant medications/significant non-drug therapies CRF.

9. Discontinuation and Replacement of Subjects and Major Protocol Deviations

9.1 Definition of Early Termination from the Study

A patient who discontinues the study before completing the Follow-Up visit at Week 28 is considered to have terminated early. All subjects who discontinue the study prior to completing the final Follow-Up visit should return to the site 28 (±2) days after the last dose of study drug or prior to this if necessary. If early termination occurs more than 28 days after the last dose of study drug, then perform the Early Termination Visit as soon as possible.

9.2 Definition of Study Completion

A patient who completes visits through the end of the Follow-Up visit at Week 28 will be recorded as having completed the study.

9.3 Early Discontinuation of Study Drug

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

- Patient withdrawal of consent
- AE that, in the opinion of the Investigator, results in it being in the best interest of the patient to discontinue study treatment
- Protocol deviation requiring discontinuation of study treatment

If a patient is withdrawn from treatment due to an AE, the patient will be followed by the Investigator as noted in Section 9.4.

All subjects who discontinue study treatment should return to the site 28 (±2) days after the last dose of study drug for procedures listed under Post-Treatment Follow-Up.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

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

9.4 Withdrawal of Subjects from Study

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

- An AE or SAE that, in the judgment of the Investigator, requires withdrawal due to its nature, severity, or required treatment, regardless of the causal relationship to treatment
- Major protocol deviations as determined by the Medical Monitor, including significant non-compliance, or loss to follow-up
- Occurrence of an exclusion criterion which is clinically relevant and affects the patient's safety or integrity of the study data, if discontinuation is considered necessary by the Investigator and/or Medical Monitor
- Serum transaminases (ALT and/or AST) >3 × ULN AND total bilirubin >2 × ULN (confirmed by repeat testing) without an alternative explanation
- Elevation of ALT or AST >3 × ULN (confirmed by repeat testing) with the appearance or worsening of symptoms felt by the Investigator to be potentially related to hepatic inflammation, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia
- Use of a non-permitted concomitant drugs and treatments, as defined in Section 8.3.10 as determined by the Medical Monitor.
- Withdrawal of the patient's consent
- Participation in any other trial during the duration of this trial as determined by the Medical Monitor.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Lack of efficacy
- Study terminated by sponsor
- Discretion of the Investigator

If a patient is withdrawn from treatment due to an AE, the patient will be followed and treated by the Investigator until resolved or stable.

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

9.5 Replacement of Subjects

Subjects who do not meet all eligibility criteria at Screening, or who qualify at Screening but are not enrolled, may be assigned a PID number and rescreened once. Patient 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.

Enrolled subjects who withdraw from the study may be replaced at discretion of the Investigator and consultation with the sponsor.

9.6 Termination of study

The Medical Monitor in collaboration with the Investigators will review the safety data on an ongoing basis throughout the study and will on a continuous ongoing basis evaluate the risk-benefit ratio. The monitoring will focus on emerging safety profile and if a positive or neutral risk-benefit ratio is not present, the study may be interrupted or terminated. If a patient experiences a Grade IV toxicity reaction (according to the CTCAE), an immediate reevaluation of the risk-benefit ratio will be performed.

10. Visit Schedule and Assessments

Table 3 shows the schedule of assessments by study visit. Subjects should be seen for all visits on the designated day or as close to it as possible.

Subjects discontinuing the study drug before completing the 12-week treatment period, and those who prematurely withdraw from the study for any reason, should be scheduled for an early termination visit as soon as possible, at which time all of the assessments listed for the final visit will be performed.

Subjects who discontinue AK002 treatment also should return for the final assessments. If they refuse to return or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the use of rescue medication and to complete the [redacted].

At a minimum, they will be contacted for safety evaluations during the 28 days following the last dose of AK002, including the final contact at the 28-day point. Documentation of attempts to contact the patient should be recorded in the patient record.

All data obtained from the assessments listed in Table 3 and described in detail in the protocol must be supported in the patient's source documentation.

Table 3 Schedule of Assessments

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.
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]	x	x	x	x	x	x	x	x
[redacted]		x	x	x	x	x	x	x
[redacted]		x	x	x	x	x	x	x
Trigger threshold test (PCE 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 3 Schedule of Assessments cont.

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 cont.

e) Subjects will be administered only the instruments that are relevant to their condition (see Table 4). 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 10.5.2.

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).

t) Subjects in the CholU, UF, and CSU-XOLAIR® (omalizumab) failure cohorts who received all 6 infusions of AK002, were followed through Day 155, and demonstrated severe symptoms of urticaria following discontinuation of treatment will be eligible to receive extended dosing with up to 12 additional doses of AK002 (see Appendix 2). For extended dosing, 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).

10.1 Information to be Collected on Screening Failures

All subjects who have signed informed consent but not entered into the study will have the study phase completion page for the screening epoch, demographics, inclusion/exclusion, patient visit dates and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the Investigator and collected only in the source data.

10.2 Patient Demographics/Other Baseline Characteristics

Patient demographic and baseline characteristic data to be collected on all subjects include date of birth, age, sex, race, and ethnicity. Smoking habits will be evaluated. Relevant medical history/current medical condition present before signing the informed consent will be captured. Where possible, diagnoses, and not symptoms, will be recorded. Any history of atopic disease (dermatitis, rhinitis and asthma) will be collected.

10.3 Treatment Exposure and Compliance

AK002 will be administered as an intravenous (IV) infusion at a dose of 0.3 mg/kg given over a period of approximately 4 hours on study Day 1. If well tolerated, dose will be increased to 1 mg/ kg, given over a period of 4 hours 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 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 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.

Administration of study drug should be recorded in the source documents and the corresponding eCRF for each administration.

10.4 Efficacy Assessments

A number of cohort-specific efficacy variables will be assessed during the study. Several patient-reported outcome (PRO) instruments are disease-specific, and subjects will be administered only the instruments that are relevant to their condition (Table 4).

Table 4 PRO Instruments for Efficacy Assessment

PRO Instrument	CholU	UF	CSU
Diary/Patients Diary Assessments (UPDD)	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]

10.4.1 Urticaria Patient Daily Diary

All subjects will be provided with an Urticaria Patient Daily Diary (UPDD). The subjects will receive clear instructions on the completion of the diary. UPDD includes CholUAS7 (itch, hives and elicitors) for CholU subjects or UAS7 (itch and hives) for UF and CSU subjects for clinical symptoms, and activity interference. Subinvestigators and subjects will receive appropriate training and guidance on the use of the Diary.

10.4.2 Urticaria Control Test

The urticarial control test (UCT) is an instrument that is valid in all types of chronic urticaria, not only for CSU, and it can also be used in urticaria subjects suffering from recurrent angioedema. The UCT is a 4-item questionnaire for assessing CU disease activity retrospectively over the previous 4 weeks. Each item is rated on a Likert-type scale (0 = very often to 4 = not at all) and a total score is calculated (range, 0 to 16; higher scores indicate better disease control; scores ≥12 are consistent with well-controlled disease. The higher the achieved score, the higher the level of disease control.

UCT complete response is defined as a score of 16. Clinically relevant response is defined as improvement of 3 or more points in the UCT score (minimal clinically important difference [MCID]). The UCT total score will not be calculated when >1 item within the questionnaire is missing.

10.4.3 [redacted]

[redacted] is the first disease-specific [redacted] questionnaire for [redacted]. It contains [redacted] each that are scored from 0 to 4 and relating to overall functioning (including work, physical, leisure and social activities), sleep, itching/embarrassment, mental status, swelling/eating, and limits

looks (limitations in choice of clothing or cosmetics used due to [redacted]). The recall period is 2 weeks. Total scores range from 0 to 100, with higher scores indicating [redacted]. [redacted] total score will not be calculated when >5 items within the questionnaire are missing.

10.4.4 [redacted]

[redacted] is a disease-specific [redacted] questionnaire for [redacted]. It consists of [redacted] items that can be grouped into domains. In addition to domain scores, it is possible to compute a total score. For score computation, the raw domain and raw total scores are transformed into percentage scores, indicating the location of the raw scores in relation (in percent) to its maximum possible score (linear transformation).

Accordingly, the minimum and highest possible domain and total score are 0 and 100, respectively.

10.4.5 [redacted]

For subjects with [redacted], the [redacted] is the first disease-specific [redacted] questionnaire for [redacted]. It consists of [redacted] items. In addition to domain scores, it is possible to compute a total score. Accordingly, the minimum and highest possible domain and total score are 0 and 100, respectively.

10.4.6 [redacted]

[redacted] is the first specific [redacted] questionnaire for all subjects that also have [redacted]. It consists of [redacted] items that can be grouped into 2 domains. In addition to domain scores, it is possible to compute a total score. Accordingly, the minimum and highest possible domain and total score are 0 and 100, respectively.

10.4.7 [redacted]

[redacted] is a [redacted]-specific health-related quality of life measure. Subjects rate their [redacted] symptoms as well as the impact of their [redacted] on various aspects of their lives. 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 subjects with CSU has been estimated to be [redacted].

10.4.8 [redacted]

[redacted] is the sum for 7 days of the daily [redacted] and the daily [redacted] multiplied by intensity of [redacted] The possible range of the weekly CholUAS7 score is [redacted].

Complete [redacted] response is defined as [redacted]=0 or by reduction of ≥90%.

10.4.9 [redacted]

[redacted] is the sum for 7 days of the daily [redacted] and the daily [redacted]. The possible range of the weekly [redacted] score is [redacted].

Complete [redacted] response is defined as [redacted] or by reduction of ≥90%.

10.4.10 [redacted]

[redacted] will be recorded by all subjects once daily in their Diary, on a scale of [redacted] (Table 5). A weekly [redacted] is derived by adding up the average daily scores of the 7 days preceding the visit. The possible range of the weekly score is therefore [redacted].

A complete [redacted] response is defined as [redacted] = 0.

Table 5 [redacted]

[redacted]

10.4.11 Symptom-Free Days

Symptoms will be recorded by the patient in their Diary. Symptom-free days (as defined in the SAP) per week or month can be calculated.

10.4.12 Skin Biopsies

Skin biopsies are optional and will be obtained at the sites in Germany.

Two skin biopsies will be obtained:

1) Visit 2 (Baseline, pre-dose), non-lesional skin
2) Visit 8 (Week 22), non-lesional skin

Skin biopsies will be obtained using a 6-mm disposable punch pre-dose and post-dose as indicated above. Biopsy areas will be cleaned with an appropriate disinfectant, considering the nature of the patient's skin. The skin will be numbed using an anesthetic injection. Each biopsy specimen will be immediately transferred into a 10 mL plastic tube containing approximately 4% neutral buffered formalin, pH 7.4. Hemostasis will be secured by pressure with gauze and suturing the wound. The sutured biopsy site will be covered by sterile patch. The biopsies will be embedded in paraffin and sectioned, and the tissue sections will be stained with monoclonal antibodies and analyzed by immunohistochemistry. Additional biopsy may be conducted in case of relapse of disease.

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

10.4.13 Laboratory Evaluations for Efficacy

A venous blood sample is to be collected and sent to the laboratory at every treatment visit and during the follow-up period. The last blood sample will be collected on the last follow up visit. Samples will be assessed for total IgE, absolute basophil and eosinophil counts, and eosinophil cationic protein (ECP).

A total of six 0.5 mL serum samples will be stored at -80°C at the study site for post hoc analysis of exploratory biomarkers. Two 0.5 mL plasma samples will be collected at Baseline and Week 22 and stored at -80°C at the study site for post hoc analysis.

10.4.14 Trigger Threshold Tests (FricTest® and Pulse-Controlled Ergometry)

A number of cohort-specific assessments will be used during the study. Instruments are disease-specific and subjects will be administered only the instruments that are relevant to their condition.

- The FricTest® will be used for diagnosing patients with symptomatic UF and for measuring their trigger thresholds and disease activity.
- Pulse-controlled ergometry testing will be used to diagnose CholU and measure trigger thresholds.

10.4.15 Measuring Disease Activity and Functional Status

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

- The [redacted] will be used to determine disease activity in subjects with recurrent [redacted] independent of its underlying causes. Subjects will use the [redacted] for [redacted] should be completed starting at Screening if the subject has a history of [redacted] at Screening.
- The [redacted] and [redacted] scoring systems will be used to assess disease activity.

10.5 Safety Assessments

10.5.1 Medical Monitoring

Dr. [redacted] should be contacted directly using the phone numbers and/or email address below to report medical concerns or for questions regarding safety.

Allakos Medical Monitor

[redacted], MD, PhD

Phone: [redacted]

Email: [redacted]

10.5.2 Physical Examination

At screening (Visit 1) and other visits indicated on the Schedule of Assessments (Table 3), a complete physical examination will be obtained as follows:

- General appearance
- Hair and skin
- Lymphatics
- Head
- Eyes
- Ears, nose and throat
- Thyroid
- Respiratory
- Cardiovascular
- Abdomen
- Musculoskeletal
- Mental status
- Neurological
- Extremities

In addition, 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). The patient's atopic disease (dermatitis, rhinitis and/or asthma) will be determined and followed during the course of the study.

10.5.3 Vital Signs

Supine vital signs include blood pressure (BP) and pulse measurements. Systolic and diastolic blood pressure will be measured using a validated device with an appropriately sized cuff. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

10.5.4 Height and Weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

10.5.5 Laboratory Evaluations for Safety

A venous blood sample is to be collected and sent to the central laboratory at every treatment visit. The last blood sample will be collected on the last follow-up visit.

Note: In the case of an Infusion-Related Reaction (IRR), a 10 mL blood sample must be collected within approximately 2 hours from the onset of symptoms for exploratory analysis.

10.5.6 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured. Coagulation will be assessed by International Normalized Ratio (INR).

10.5.7 Clinical Chemistry

Albumin, protein, glucose, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin[#], direct bilirubin, gamma-glutamyltransferase (GGT), albumin, creatinine kinase, chloride, calcium, sodium, potassium, magnesium, lactate dehydrogenase (LDH), creatinine, inorganic phosphorus, urea/BUN, uric acid, hs-CRP, fT3*, fT4* and total IgE will be measured.

Notes: #If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

*fT3 and fT4 measured at Screening only.

10.5.7.1 Follicle-Stimulating Hormone

A serum pregnancy test will be obtained at Screening (Visit 1) for all female subjects of childbearing potential. At Screening, follicle-stimulating hormone (FSH) will be tested on females to confirm post-menopausal status (FSH level >40 mIU/mL).

10.5.7.2 Serology

Blood will be obtained at Screening for serology tests, including hepatitis B surface antigen (HBsAG), hepatitis C antibody, hepatitis B core antibody (anti-HBc), and human immunodeficiency virus (HIV).

10.5.7.3 Anti-Drug-Antibodies

Blood will be collected for determination of anti-drug antibodies (ADA) before the first dose at Day 1 (Visit 2), Day 29 (Visit 3), Day 85 (Visit 5), Day 155 (Visit 8), and Day 197 (Visit 10) at the study center. An unscheduled blood sample for ADA may be obtained if a related adverse event suspected of being associated with immunogenicity occurs.

10.5.7.4 PK Analysis

PK will be analyzed retroactively if possible, using back up blood samples at the following timepoints- before the first dose at Day 1 (Visit 2), Day 29 (Visit 3), Day 85 (Visit 5), Day 155 (Visit 8), and Day 197 (Visit 10)/End or Study/Early Termination).

10.5.8 Urinalysis

A midstream urine sample (approximately 30 mL) will be obtained in order to avoid contamination with epithelial cells and sediments and allow proper assessments. Semi-quantitative “dipstick” evaluation for specific gravity, glucose, protein, bilirubin, ketones, leukocytes and blood will be performed at site. When a dipstick evaluation is abnormal, e.g., positive for WBC and/or blood, a urine sample needs to be sent to the lab for microscopic examination including RBC and WBC. Details on collection of urine for analysis are provided to Investigators in the Laboratory Manual.

10.5.8.1 Urine Drug Screen and Cotinine Test

Urine samples will be collected at Screening for urine drug screening (alcohol, amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine, methadone, methaqualone, opiates, phencyclidine) and urine cotinine tests.

10.5.9 Fecal Collection

Fecal collection kits will be provided to subjects during Screening for ova and parasite tests. Subjects will return the sample to the clinical site during the Screening period (Days -28 to -7).

10.5.10 Electrocardiogram

Standard 12 lead electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is: ECG collection first, followed by vital signs, and blood sampling. The

ECGs will be recorded at Visits 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. The print-outs will be generated and kept at the Investigator site as source documentation. Clinically significant ECG findings prior to dosing with AK002 must be reviewed by the Principal Investigator and/or cardiologist. Clinically significant abnormalities should be recorded on the relevant section of the Medical History/Current Medical Conditions/AE CRF page, as appropriate.

10.5.11 Pregnancy Testing

All women of childbearing potential will have a serum pregnancy test and urine pregnancy tests at the visits specified in Table 3. A positive urine pregnancy test requires immediate interruption of study medication until serum B-hCG is performed and found to be negative. If positive, the patient must be discontinued from the study. Urine pregnancy test kits will be provided to the sites by the Central Lab.

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

10.5.12 Tolerability/Acceptability

Other than adverse events, no specific tolerability/acceptability data are collected.

10.6 End of Trial

End of trial is defined as last patient, last visit.

11. Adverse Event Reporting

All adverse events will be collected starting from the time of first AK002 infusion and until the end of the follow-up period or the Early Termination Visit, unless directed otherwise by Allakos.

In accordance with 21 Code of Federal Regulation (CFR) 312.32(b) and International Conference on Harmonisation (ICH) Guidance E2A, an AE is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or

frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected prior to first study drug infusion that do not worsen.
- Significant reductions in numbers of eosinophils or basophils in blood count, as these are expected therapeutic effects of the study drug.

11.1 AE Recording

At each evaluation, the Investigator or designee will determine whether any AEs have occurred. The assessment of an AE will be done pursuant to definitions set forth by ICH/Good Clinical Practice (GCP) guidelines and other applicable regulatory requirements. The patient will be questioned in a general manner and no specific symptoms will be suggested (e.g., ask the patient if he/she has had have had any "changes in health" since the last visit or assessment).

Any initial information discovered by the Investigator or designee (i.e., complaint[s] and known start/end dates and times) will be documented. The Investigator or designee will assess the initial AE finding(s) to determine if the medical occurrence is in fact an AE by officially documenting the condition/diagnosis on the AE form.

Action taken will be categorized as none, study drug permanently discontinued, dose modified, required concomitant medication, and/or other.

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

11.2 AE Severity

AEs are to be recorded on the AE page of the eCRF. Severity will be graded according to the following definitions as listed in Table 6 as well as the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

When the intensity of an AE changes more than once a day, the maximum severity for the event should be listed. If the intensity changes over a number of days, these changes should be recorded separately (i.e., as having distinct onset dates).

Table 6 Adverse Event Severity Grading

Grade	Severity	Description
1	Mild	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The patient may be aware of the sign or symptom but tolerates it reasonably well.
2	Moderate	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
3	Severe	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
4	Life-threatening	The patient is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.
5	Death	Any adverse event where the outcome is death.

11.3 AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 7.

Table 7 Adverse Event Relationship to Study Drug

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

11.4 Adverse Events of Special Interest

Selected non-serious and serious adverse events that meet criteria for classification as an Adverse Event of Special Interest (AESI) must be recorded in the eCRF, regardless of the Investigator's assessment of relationship to the study drug. Beginning from the time of first study drug infusion and ending at Day 197 or the ET Visit (unless directed otherwise by Allakos), any

new AESI (or new information related to a previously reported AESI) must be recorded in the AE eCRF and designated as an "adverse event of special interest". Information regarding date of event onset, event severity grading, action taken in response to event, investigator assessment of relationship to study drug, investigator assessment of seriousness, relevant laboratory, pathology, or radiology assessments, event outcome, and date of event resolution will be collected. The Medical Monitor will review data relating to safety during the study, including following the occurrence of AESIs to determine if specific action needs to be taken. The Medical Monitor may also request additional information (not described above) be provided.

Adverse Events of Special Interest for this trial include:

- Malignancies confirmed by histopathological report
- Parasitic infections confirmed by positive clinical laboratory test
- Opportunistic infections (infections known to be more severe or occur more frequently in immunosuppressed populations) as confirmed by positive clinical laboratory test
- Infusion and hypersensitivity reactions, including anaphylaxis.

An AESI that also qualifies as a SAE must also be reported as a SAE. AESIs that are also SAEs must be recorded in the AE eCRF and designated as both "serious" and as an "adverse event of special interest."

Note: If an IRR causes the infusion to be interrupted or slowed, a blood sample (approximately 5 mL serum and 5 mL plasma) must be collected within approximately 1–2 hours from the onset of symptoms for Exploratory Safety Analysis.

11.5 Serious Adverse Events

Serious adverse events will be recorded beginning with the signing of the informed consent form and ending at the end of the follow-up period or the Early Termination Visit unless directed otherwise by Allakos. SAE collection in the period after signing the informed consent and before the first study drug infusion will be limited to SAEs that are related to Screening activities. All SAEs will be collected starting at the time of the first infusion of study drug.

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening AE; the patient is at risk of death at the time of the event. It does not refer to an event that hypothetically might cause death if it were more severe.

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the patient or require intervention to prevent one of the outcomes listed.

Note: Medical and scientific judgment should be exercised in deciding whether SAE reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above (including suspected transmission of an infectious agent by a medicinal product should be reported as an SAE). Any AE is considered an SAE if it is associated with clinical signs or symptoms judged by the Investigator to have a significant clinical impact.

Inpatient hospitalization for the purpose of study drug infusion will not be reported as a serious adverse event in this trial.

11.6 Adverse Event Reporting Procedures

11.6.1 All Adverse Events

Any clinically significant adverse event that is ongoing at the time of study completion or early termination will be followed by the investigator until event resolution, the adverse event is otherwise explained or not considered clinically significant by the investigator.

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy.

All AEs identified, whether serious or non-serious, will be recorded in the eCRF until Day 197 or Early Termination.

All AEs, regardless of seriousness, severity, or presumed relationship to investigational product, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., dysuria, urinary nitrites should be reported as a urinary tract infection). The Investigator must record in the eCRF his or her opinions concerning the relationship of the AEs to the study drug.

Subjects (or their designees, if appropriate) must be provided with a "study card" indicating the name of the investigational product, the study number, the Investigator's name, and a 24-hour emergency contact number, and excluded concomitant medications.

11.6.2 Serious Adverse Event Reporting

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

Serious adverse events must be reported to:

[redacted], MD, PhD

[redacted]

Phone: [redacted]

Fax: [redacted]

Email: SAE@allakos.com

Serious adverse event report forms will be provided to the investigational site to assist in collecting, organizing, and reporting SAEs and follow-up information will be completed within 24 hours. SAEs should also be recorded in EDC on the AE eCRF and designated as "serious."

The site will notify the Institutional Review Board (IRB)/ local authorities according to its guidelines. All SAE report forms will be completed within 24 hours. All efforts will be made to obtain accurate and complete medical records for the SAE.

The patient's condition will be followed by the Investigator or designated Sub-investigator until resolution of the condition or a return to baseline levels. If additional visits are required, the patient will be asked to return to the study site for further follow-up. If condition is still ongoing at the time the patient exits the study, every effort will be made to continue to follow up with the patient for a reasonable period of time, or until there is a return to baseline or stabilization of the condition. As additional information becomes available, such as hospital discharge notes and patient medical records, the Investigator will be notified and provided with all relevant information.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient's participation in the study, must be followed until any of the following occurs:

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

11.6.3 Pregnancy Reporting

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

The Investigator must report any pregnancy to Allakos, Inc. within 24 hours of becoming aware of it using the provided pregnancy reporting forms. The patient must be immediately discontinued from study drug. An uncomplicated pregnancy will not be considered an AE or SAE, but all pregnancies will be followed through term.

Pregnancies are captured if they occur in female subjects or in the sexual partners of male subjects from the time the patient is first exposed to the study drug until 120 days after last dose received.

Any congenital abnormalities noted at birth in the offspring of a patient who received study drug will be reported as an SAE. The outcome of any pregnancy and the presence or absence of any congenital abnormality will be recorded in the source documentation and reported to the Medical Monitor and Sponsor.

11.7 Anaphylaxis

Signs or symptoms of anaphylaxis will be carefully monitored and treated according to standard of care. In addition, as part of the anaphylaxis assessment, a sample of blood should be obtained for plasma histamine and tryptase level within 1 hour of the onset of the symptoms. Emergency crash cart equipment and medications, including multiple doses of epinephrine, pressors, and bronchodilators, will be available at all times during the conduct of the study. To define anaphylactic reactions in a consistent and objective manner, all AEs of suspected anaphylaxis will be evaluated using the criteria specified in Appendix 1.

11.8 Medical Monitoring

Dr. [redacted] should be contacted directly using the phone numbers and/or email address below to report medical concerns or for questions regarding safety.

Allakos Medical Monitor

[redacted], MD, PhD

Phone: [redacted]

Email: [redacted]

12. Data Review and Database Management

12.1 Site Monitoring

The Investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the eCRFs, which will be documented as being the source data. The Investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12.2 General Safety Monitoring

The Investigators and Medical Monitor will review data relating to safety and to conduct of the study.

The trial must be discontinued prematurely in the event of any of the following:

- A life-threatening AE that is possibly or probably related to treatment
- A fatal AE that is possibly or probably related to treatment

- New information leading to unfavorable risk-benefit judgment of the study drug, e.g., occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or other unfavorable safety findings
- >50% of subjects at any time have been withdrawn due to drug-related AEs, including those related to abnormal laboratory results, or other safety findings
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely
- Discontinuation of development of the Sponsor's study drug

Health Authorities and IECs will be informed about the discontinuation of the trial in accordance with applicable regulations. The trial may be terminated or suspended upon request of Health Authorities.

13. Data Analysis

This section outlines the statistical methods to be used for the analysis of the data from the study. A separate Statistical Analysis Plan (SAP), which will be completed and signed off prior to data base lock.

When the SAP differs from analyses described in the protocol, the SAP will take precedence.

Continuous variables will be summarized using number of non-missing observations, mean, standard deviation (SD), median, minimum, and maximum; categorical variables will be summarized using the frequency count and the percentage of subjects in each category.

Baseline for data analysis is defined as the last assessment prior to the first infusion of the study drug.

The primary summaries will be based on individual cohorts and the data from all 3 cohorts combined, wherever possible.

13.1 Populations for Analysis

13.1.1 MITT 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 of the primary efficacy variable UCT.

13.1.2 Safety Population

The safety population will consist of all subjects who are enrolled, have received at least one dose of study drug.

13.1.3 Per-Protocol Population

The per-protocol (PP) population will consist of all subjects from the MITT-population for whom no major protocol violations adversely affecting the data interpretation are reported.

13.2 Disposition of Subjects

The number of subjects who signed the informed consent, received a dose of study drug, completed, or discontinued from the study and the reason for study discontinuation will be tabulated.

13.3 Protocol Deviations

Major protocol deviations will be summarized. Subjects with major protocol deviations affecting an efficacy evaluation will be excluded from the PP population.

13.4 Patient Demographics/Other Baseline Characteristics

Descriptive statistics of subject characteristics and baseline values will be presented for all populations (total and by cohort).

13.5 Treatments (Study Drug, Concomitant Therapies, Compliance)

Exposure to study drug will be summarized descriptively. The use of rescue medication is part of the efficacy assessment and will be reported there. Other concomitant therapy used both prior to and after start of study drug administration will be summarized. The WHO Drug Dictionary will be used for coding of medications.

13.6 Analysis of the Primary Objectives

13.6.1 Primary Efficacy Variable

The primary variable is the change from baseline in UCT score. This variable will be summarized using descriptive statistics of mean, median, minimum, and maximum at Weeks 4, 8, 12, 16, 20, 24, and 28. A 95% confidence interval for the mean will be computed. The summaries will be provided for all 3 cohorts combined as well as for each individual cohort.

Additionally, subjects achieving complete response (CR: defined as the total UCT score = 16) will be summarized with number and percent of subjects for each visit. Subjects achieving 0, 1, 2, 3, and 4 CRs over the 7 post-baseline visits will also be summarized. Refer to the SAP for additional information.

13.7 Analysis of Secondary Objectives

13.7.1 Secondary Efficacy Variables

The [redacted], and weekly number of symptom-free days will be summarized analogous to the primary endpoint, as a mean difference from Baseline (Visit 1) to weeks 4, 8,12, 16, 20, 22, 24, and 28.

Number and percent of subjects receiving rescue medication will be summarized.

13.7.2 Safety

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). The treatment-emergent adverse events (TEAEs) will be summarized by the number and percentage 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 summary by relationship, and the AE of the most severe grade will be included in the summary by severity table.

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).

Laboratory data will be summarized by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) and by presenting number and percentage of subjects with notable laboratory abnormalities.

Data from other tests (vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

All safety and tolerability endpoints will be summarized. Baseline for all safety endpoints will be defined as the last recorded observation before the administration of AK002.

13.8 Sample Size Calculation

There is no formal statistical hypothesis testing specified for this study; this study is primarily designed to begin the characterization of the effect and safety and tolerability profile of AK002 in subjects with CU. However, a total of 40 patients is typical for a first-in-indication study and should be adequate to pick up major safety signals should such signals indeed exist.

14. Data Collection, Retention and Monitoring

14.1 Data Collection Instruments

All staff at the study site will adhere to Good Documentation Practices. Data will be entered into CRFs using source document data. Source documents may include, but are not limited to laboratory data, recorded data from automated instruments, medical progress notes, and e-mail correspondence.

14.2 Data Management Procedures

Data collection will be performed in accordance with Good Documentation Practices. Data will be entered into eCRFs using source document data. Source documents may include, but are not limited to laboratory data, recorded data from automated instruments, medical progress notes, and e-mail correspondence. The standard procedures for handling and processing records will be followed per GCP and the data management standard operating procedures. A comprehensive Data Management Plan will be developed and approved by the Sponsor.

14.3 Data Quality Control and Reporting

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

14.4 Archiving of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained.

Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

14.5 Availability and Retention of Investigational Records

In accordance with 21 CFR 312.62(c) and ICH/GCP 4.9.5 and all other applicable regulatory requirements, following completion or termination of the study, copies of all study records with limited access storage room, will be retained for a minimum of 2 years after notification that the investigations have been discontinued and the FDA has been notified, or for 2 years after all marketing applications have been approved.

The trial master file will be created during the implementation phase of a study, maintained on an ongoing basis throughout the duration of the project and collated at the end of the study. The files will contain folders that may include, but are not limited to, the following subcategories:

- Financial agreements
- Regulatory documents
- Independent ethics committee (IEC) Documents
- Drug Accountability
- Correspondence
- Medical Reports
- Patient Data
- Monitoring Visit Reports
- Sample CRFs and CRF

14.6 Data Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the United States CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

14.7 Patient Confidentiality

Only the patient number, patient initials, and demographics will be recorded in the eCRF. If the patient name appears on any source document collected by the Sponsor (e.g., hospital discharge summary), it must be removed from the document and the patient number and patient initials recorded on the source document before the document is transmitted to the Sponsor. All study findings will be stored in electronic databases. The subjects will give explicit written permission for representatives of the Sponsor, regulatory authorities, and the IEC to inspect their medical records to verify the information collected. Subjects will be informed that all personal

information made available for inspection will kept confidential and to the extent permitted by all applicable state, local, and federal data protection/privacy laws and/or regulations and will not be made publicly available. If the results of the trial are published, the patient's identity will remain confidential.

All study subjects will be advised not to share their study information with other subjects.

15. Administrative, Ethical, and Regulatory Considerations

The study will be conducted in a manner consistent with the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), IEC (21 CFR 56 and ICH E6), and Obligations of Clinical Investigators (21 CFR 312 and ICH E6). The Investigator must also comply with all applicable privacy regulations (e.g., the Health Insurance Portability and Accountability Act [HIPAA], European Union Data Protection Directive 95/46/EC).

15.1 Protocol Amendments

An amendment must be agreed to in writing by Allakos, Inc. and submitted to the health authority as a Clinical Trial Application/Investigational New Drug (IND) amendment. Protocol amendments cannot be implemented without prior written IEC approval except as necessary to eliminate immediate safety hazards to subjects. Written approval of a protocol amendment is not required prior to implementation of changes to the protocol that eliminate immediate hazard to the patient; however, approval must be obtained as soon as possible thereafter. Any agreed amendments must also be signed by the Principal Investigator.

15.2 Institutional Review Board/Independent Ethics Committees

The protocol and ICF will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. All SAEs, regardless of causality, will be reported to the IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

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

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

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

15.3 Informed Consent Form

Prior to screening, all subjects must consent to participate.

In accordance with ICH GCP Guidelines E6 Section 4.3.3, subjects will be asked whether or not they would like their PCP notified of their study participation.

The process of obtaining the informed consent will be in compliance with all federal regulations, ICH requirements, and local laws.

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

In addition, prior to undergoing biopsies, subjects will provide informed consent in accordance with the standard operating procedures and policies of the investigational sites.

15.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and authors. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, HIPAA.

15.5 Clinical Trial Registration

This clinical trial will be registered on the "clinicaltrials.gov" clinical trial registry website as required by 121 STAT. 823.

15.6 Payment to Subjects

All subjects may be compensated for participating in this study, in accordance with the payment amounts per study day stated in the patient's signed ICF approved by the local IRB/IEC. No compensation beyond what is stated in the ICF is permitted.

15.7 Investigator's Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

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

2) Personally conduct or supervise the study (or investigation).

3) Ensure that the requirements relating to obtaining informed consent and IEC review and approval meet federal guidelines.

4) Report to the Sponsor or designee any adverse events that occur in the course of the study, in accordance with 21 CFR 312.64 and ICH E2A.

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

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

7) Ensure that an IEC that complies with the requirements of 21 CFR part 56 and ICH E6 will be responsible for initial and continuing review and approval of the clinical study. Promptly report to the IEC all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).

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

9) Comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements listed in 21 CFR Part 312.

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17. Appendices

17.1 Appendix 1: Sampson's Criteria for Anaphylaxis

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

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

OR

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

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

17.2 Appendix 2: Procedures for Extended Dosing (Optional)

Summary of Extended Dosing

Subjects in the CholU, UF, and CSU-XOLAIR® (omalizumab) failure cohorts who received all 6 infusions of AK002, were followed through Day 155, and demonstrated severe symptoms of urticaria following discontinuation of treatment will be allowed the option to receive extended dosing with up to 12 additional doses of AK002.

For extended dosing, 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.

Extended dosing will include a Screening Period of 2 to 3 weeks, a Treatment Period of 44 weeks, and a Follow-up Period of 8 weeks after the last dose of study drug. During the Screening Period, subjects will receive a standard oral dose of a second-generation H1-antihistamine once daily, with on-demand dosing of up to 3 additional tablets per day. During the Treatment Period, subjects will continue daily dosing with the second-generation H1-antihistamine (standard dose once daily with on-demand dosing of up to 3 additional tablets per day) and AK002 administered by IV infusion on Extended Dosing Days 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, and 309. Subjects will be followed for 8 weeks after the last dose of study drug (Follow-up Period). Safety assessments and response to study drug will be evaluated throughout the study. The optional extended dosing period is outlined in Table 8.

Table 8 Extended Dosing Period

Description	Screening Period	Treatment Period AK002 Dose (mg/kg)†												Follow-up Period
		0.3	1	1	3*	3*	3*	3*	3*	3*	3*	3*	3*	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Week	-3 to -2	0	4	8	12	16	20	24	28	32	36	40	44	52
Extended Dosing Day	-21 to -14	1	29	57	85	113	141	169	197	225	253	281	309	365

* Increase to 3 mg/kg if UCT score is <12 and/or at the discretion of the Investigator in consultation with the Allakos Medical Monitor. If UCT score is ≥12, and if the Investigator in consultation with the Allakos Medical Monitor thinks that the subject has experienced adequate symptom improvement, then continue with the 1 mg/kg dose. 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.

† The Investigator in consultation with the Allakos Medical Monitor, can chose to maintain the patient's last administered dose depending on how much time has lapsed between Week 20/last dose under main study and first dose under extension.

Based on the subject's weight, the designated clinical staff will prepare the appropriate dilution of AK002 for IV administration at 0.3 mg/kg for Extended Dosing Day 1, 1 mg/kg for Extended Dosing Days 29 and 57, and either 1 mg/kg or 3 mg/kg (depending on UCT score and Investigator discretion) for Extended Dosing Days 85, 113, 141, 169, 197, 225, 253, 281, and 309.

The Investigator in consultation with the Allakos Medical Monitor, can chose to maintain the patient's last administered dose depending on how much time has lapsed between Week 20/last dose under main study and first dose under extension.

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.

Objective

To evaluate the long-term safety and tolerability of up to 12 additional doses of AK002 in subjects with CU.

Entry Criteria

Inclusion Criteria

1) Adults (≥18 and ≤85 years old)

2) Body weight <125 kg

3) Provide signed and dated informed consent

4) Enrolled in either the CU, UF, or CSU-XF cohorts

5) Completed 6 infusions of AK002 and with follow-up through Day 155 [Week 22]) and willing to begin extended dosing upon qualification

6) 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 post-week 22 (Day 155) and by week 44 (Day 309) i.e., within 6 months from last dose.

6) Uncontrolled CU (UCT <12) for at least 2 weeks prior to the time of enrollment into the extension

7) Able to read, understand, and willing to sign the informed consent form and comply with study procedures

8) Willing, committed, and able to return for all clinic visits and complete all study-related procedures, including willingness to have IV infusion of study drug administered by a qualified person

9) Females of childbearing potential must have a negative pregnancy test at Baseline. Female subjects must be willing to use highly effective contraception (Pearl-4 Index <1) or abstain from sexual activity from screening until the end of the study, or for 120 days following the last dose of study drug, whichever is longer. A woman will be considered not of childbearing potential if she is post-menopausal for greater than 2 years (FSH >40 mL) or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy).

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

10) No participation in clinical trials 4 weeks before participation in this study

Exclusion Criteria

1) Acute urticaria
2) Concurrent/ongoing treatment with immunosuppressives (e.g., cyclosporine, methotrexate, dapsone, or others) within 4 weeks or 5 half-lives prior to Baseline, whichever is longer
3) Significant medical condition rendering the subject immunocompromised or not suitable for a clinical trial
4) Significant concomitant illness that would adversely affect the subject's participation or evaluation in this study
5) History of malignancies within 5 years prior to screening other than a successfully treated non-metastatic cutaneous, basal, or squamous cell carcinoma and/or in situ cancer
6) Presence of clinically significant laboratory abnormalities
7) Lactating women or pregnant women
8) Substance abuse (drug or alcohol) or any other factor (e.g., serious psychiatric condition) within the last 5 years that could limit the subject's ability to comply with study procedures
9) Subjects who are detained officially or legally to an official institute or those that have been committed to an institution by an order issued either by the judicial or the administrative authorities will be excluded
10) Use of omalizumab within 2 months prior to Baseline
11) Receipt of IV IgG therapy 30 days prior to Baseline
12) Plasmapheresis 30 days prior to Baseline
13) Use (daily or every other day) of doxepin 14 days prior to Baseline
14) Receipt of inactive vaccination or live attenuated vaccine 30 days prior to Baseline
15) Use of H2-antihistamines 7 days prior to Baseline
16) Intake of leukotriene antagonists within 7 days prior to Baseline
17) Intake of systemic corticosteroids (e.g., oral or depot) within 14 days prior to Baseline
18) Positive screening for ova and parasite test at Baseline
19) Treatment of helminthic parasite within 6 months of screening

20) Positive human immunodeficiency virus serology at screening

21) Positive hepatitis serology at Baseline, except for vaccinated subjects or subjects with past but resolved hepatitis at screening

22) Donation or loss of >500 mL of blood within 56 days prior to administration of study drug or donation of plasma within 7 days prior to administration of drug

23) Known hypersensitivity to any ingredients of AK002 or drugs related to AK002 (e.g., monoclonal antibodies, polyclonal gamma globulin)

Procedures

Subjects will maintain the same patient identification number during extended dosing. Unless specified otherwise, the procedures and methods performed during the initial 6 infusions will continue through extended dosing. This includes but is not limited to fasting requirements, prohibited medications, allowed medications, rescue medications, dose preparation, dose administration, AK002 storage and accountability, dietary and lifestyle restrictions, adverse event reporting, and serious adverse event reporting.

The site will obtain written informed consent for extended dosing. All subjects who sign an informed consent for extended dosing will be recorded in the EDC. A subject is considered enrolled in extended dosing at the time for the first infusion.

The schedule of assessments for extended dosing is provided in Table 9.

General Safety Monitoring

The Investigators and Medical Monitor will review data relating to safety and conduct of the study throughout the course of extended dosing.

Study Stopping Rules

Access to extended dosing will be discontinued prematurely in the event of any of the following:

- A life-threatening AE that is possibly or probably related to treatment as determined by the Medical Monitor
- A fatal AE that is possibly or probably related to treatment as determined by the Medical Monitor
- New information leading to unfavorable risk-benefit judgment of the study drug, e.g., occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or other unfavorable safety findings

- Sponsor's decision that extended dosing is unjustifiable for medical or ethical reasons
- Discontinuation of development of AK002

Health Authorities and IRB/IECs will be informed regarding discontinuation of access to extended dosing in accordance with applicable regulations. Access to extended dosing may be terminated or suspended on request of Health Authorities.

Data Management Procedures

Data for all subjects who sign an informed consent for extended dosing will be recorded in eCRFs designated for extended dosing and will be separate from eCRFs completed for the initial 6 infusions. The database for the initial 6 infusions will be separate from the database for extended dosing, which will allow for database lock of the data obtained for the initial 6 infusions prior to completion of extended dosing. The database for extended dosing will be locked after all subjects have completed/discontinued extended dosing.

Table 9 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 9 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**
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 10.5.2.

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