CLINICAL STUDY PROTOCOL

A Double-blind, Randomized, Active-controlled, Parallel Group, Phase 3 Study to Compare Efficacy and Safety of CT-P39 and Xolair in Patients With Chronic Spontaneous Urticaria Who Remain Symptomatic despite H_1-antihistamine Treatment

PROTOCOL NUMBER CT-P39 3.1

EudraCT Number:	2020-000952-36
NCT Number	NCT04426890
Investigational Product:	CT-P39 (proposed Xolair biosimilar)
Sponsor:	CELLTRION, Inc. [redacted]
Sponsor Contact:	[redacted]
SAE Reporting:	SAE Email: [redacted]
Version and Date of Protocol:	Protocol Version 2.3, including country specific A.0, 10 August 2021

Protocol Approval

Study Title	A Double-blind, Randomized, Active-controlled, Parallel Group, Phase 3 Study to Compare Efficacy and Safety of CT-P39 and Xolair in Patients With Chronic Spontaneous Urticaria Who Remain Symptomatic despite H_1-antihistamine Treatment
Protocol Number	CT-P39 3.1
Protocol Date	Protocol Version 2.3, including country specific A.0, 10 August 2021

Protocol accepted and approved by:

[redacted]

Signature

Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled 'A Double-blind, Randomized, Active-controlled, Parallel Group, Phase 3 Study to Compare Efficacy and Safety of CT-P39 and Xolair in Patients With Chronic Spontaneous Urticaria Who Remain Symptomatic despite H_1-antihistamine Treatment' and the accompanying current Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Version 2.3, including country specific A.0, dated 10 August 2021, the International Council for Harmonisation harmonized tripartite guideline E6(R2): Good Clinical Practice, Declaration of Helsinki (World Medical Association 2013), and all applicable government regulations. I will not make changes to the protocol before consulting with CELLTRION, Inc. or implement protocol changes without Independent Ethics Committee (or Institutional Review Board) approval except to eliminate an immediate risk to patients. I agree to administer study drug only to patients under my personal supervision or the supervision of a Sub-Investigator.

I will not supply the study drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from CELLTRION, Inc.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator:

Address:

Phone:

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PROTOCOL SYNOPSIS

Protocol Number: CT-P39 3.1

Title: A Double-blind, Randomized, Active-controlled, Parallel Group, Phase 3 Study to Compare Efficacy and Safety of CT-P39 and Xolair in Patients With Chronic Spontaneous Urticaria Who Remain Symptomatic despite H_1-antihistamine Treatment

Study Phase: Phase 3

Study Centers: Approximately 65 study centers in 7 countries

Test Drug Formulation, Dose, and Regimen:
CT-P39 will be supplied in a prefilled syringe (PFS) of 1 mL solution containing 150 mg of omalizumab.
Treatment Period I
300 mg or 150 mg of CT-P39 will be subcutaneously administered using a PFS on Weeks 0, 4, and 8.
Treatment Period II
300 mg of CT-P39 will be subcutaneously administered using a PFS on Weeks 12, 16, and 20.

Reference Drug Formulation, Dose and Regimen:
European Union (EU)-approved Xolair will be supplied in a PFS of 1 mL solution containing 150 mg of omalizumab.
Treatment Period I
300 mg or 150 mg of Xolair will be subcutaneously administered using a PFS on Weeks 0, 4, and 8.
Treatment Period II
300 mg of Xolair will be subcutaneously administered using a PFS on Weeks 12, 16, and 20.

Objectives:
Primary Objectives
- To demonstrate the equivalence of CT-P39 to Xolair at a dose of 300 mg in terms of efficacy in patients with chronic spontaneous urticaria (CSU) as determined by change from baseline in weekly itch severity score (ISS7) at Week 12
- To evaluate the relative potency of CT-P39 compared with Xolair as determined by change from baseline in ISS7 at Week 12

Secondary Objectives
- To evaluate dose response in terms of efficacy between 300 mg and 150 mg for CT-P39 and Xolair
- To evaluate additional efficacy of CT-P39 and Xolair at each dose level of 300 mg and 150 mg
- To evaluate the pharmacokinetics (PK), quality of life (QoL), safety, and immunogenicity of CT-P39 and Xolair

Main Selection Criteria:
Male or female patients with a history of at least 6 months of CSU who had hives and itching for 6 consecutive weeks or more despite current use of H_1-antihistamines for this time period will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion Criteria:
Each patient must meet all of the following criteria to be randomized in this study:
1. Male or female between 12 and 75 years of age (both inclusive; age limits would depend on country-specific regulation).
2. Have been diagnosed with CSU for at least 6 months prior to the first study drug administration.
3. Must be diagnosed as CSU refractory to H_1-antihistamine defined as below:
   a) Presence of hives associated with itching for ≥ 6 consecutive weeks at any time prior to the first study drug administration despite current use of H_1-antihistamine treatment for this time period
   b) Weekly itch severity score (range 0 to 21 points) ≥ 8 points and weekly urticaria activity score (UAS7; range 0 to 42 points) ≥ 16 points in the 7 consecutive days (Day -7 to Day -1) prior to the first study drug administration
   c) Documented use of an approved dosage of nonsedating H_1-antihistamine for CSU for at least 3 consecutive days immediately prior to start of patient electronic diary (eDiary) record for baseline ISS7 (Day -7 to Day -1)
4. Has patient eDiary entries without missing data in the 7 consecutive days (Day -7 to Day -1) prior to the first study drug administration.

5. Be willing and able to complete a patient eDiary twice daily (morning and evening) throughout the study.
6. Patient and/or their legally authorized representative are informed and will be given ample time and opportunity to read and/or understand the nature and purpose of this study including possible risks and side effects and must sign the informed consent form before any specific procedures.
7. Female patient must agree to use highly effective methods of contraception consistent with local regulations throughout the study period (excluding women who are not of childbearing potential). Examples include the following:
   a) Combined (estrogen and progestogen containing) or progestogen-only hormonal contraceptives associated with inhibition of ovulation
   b) Intrauterine device or intrauterine hormone-releasing system
   c) True abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to investigational drug, and withdrawal are not acceptable methods of contraception.

   Menopausal female patients must have experienced their last period more than 1 year prior to the date of informed consent to be classified as not of childbearing potential. Male patient who is sexually active with a woman of childbearing potential must agree to use highly effective method described as above or two acceptable methods of contraception (e.g., male or female condom AND additional hormonal or barrier contraceptive method other than condom by female partner) consistent with local regulations throughout the study period. Contraception is not required if either patient or his/her partner who has been surgically sterilized more than 24 weeks prior to the date of informed consent.

Exclusion Criteria:

A patient meeting any of the following criteria will be excluded from the study:

1. Has a chronic urticaria with clearly defined underlying etiology (e.g., physical urticaria such as acute, solar, cholinergic, heat, cold, aquagenic, pressure or contact) other than CSU or any disease with symptoms of urticaria or angioedema (e.g., urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary or acquired angioedema, lymphoma, leukemia or generalized cancer).
2. Has a body weight of < 30 kg.
3. Has a medical history of and/or current disease including any of the following:
   a) History of clinically significant allergic reaction and/or hypersensitivity to any component of omalizumab, Chinese hamster ovary cell products, other recombinant human or humanized antibodies, H_1-antihistamines, or dry natural rubber (a derivative of latex)
   b) History of and/or concomitant myocardial infarction
   c) History of anaphylactic shock
   d) History of and/or concomitant immune complex disease (including allergic reaction type III), hyperimmunoglobulin E syndrome, autoimmune disease, or bronchopulmonary aspergillosis
   e) Any active skin disease associated with itch including atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, or senile pruritus
   f) A known infection with human immunodeficiency virus, hepatitis B, hepatitis C, or any active infection requiring treatment, except adequately treated and completely recovered past infections
   g) Any active malignancy or history of malignancy except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ
4. Has history of and/or a current use of medications including any of the following:
   a) Treatment with omalizumab or other monoclonal antibodies, protein, fusion protein, or other biologic agent targeting immunoglobulin E (IgE)
   b) Treatment with an investigational drug within 4 weeks or 5 half-lives (whichever is longer) prior to the first study drug administration
   c) Routine administration (i.e., daily or every other day for ≥ 5 consecutive days) of systemic glucocorticoids, hydroxychloroquine, methotrexate, cyclosporine, azathioprine, cyclophosphamide, tacrolimus, or mycophenolate mofetil within 5 weeks prior to the first study drug administration
   d) Intravenous immunoglobulin G or plasmapheresis within 5 weeks prior to the first study drug administration
   e) Regular (i.e., daily or every other day for ≥ 5 consecutive days) use of oral doxepin within 3 weeks prior to the first study drug administration

f) Use of any H_2-antihistamine or leukotriene receptor antagonist within 2 weeks prior to the first study drug administration (However, continuing H_2-antihistamine or leukotriene receptor antagonist treatment for disease other than CSU is allowed)
g) Use of beta-blocker therapy within 2 weeks prior to the first study drug administration
h) Use of H_1-antihistamines at greater than approved doses from 3 days prior to the start of patient eDiary record for baseline ISS7 (Day -7 to Day -1)

5. Diagnosed with parasitic diseases or colonization on stool evaluation for ova and parasites (stool ova and parasite examination should be performed in patients who meet both the following criteria):
   a) Correspond to any of risk factors for parasitic disease
      - Travel within 6 months prior to the first study drug administration or living in an endemic area of parasitic infections
      - Chronic gastrointestinal symptoms
      - Chronic immunosuppression
   b) Absolute eosinophil count > 2 × upper limit of normal
6. Unable to receive background therapy and rescue therapy with protocol-defined H_1-antihistamines or contraindicated to epinephrine or other components of these agents as per Investigator's discretion.
7. Has ongoing or a history of alcohol or drug abuse within 6 months prior to the first study drug administration.
8. Female patient who is currently pregnant or breastfeeding, or plans to become pregnant or breastfeed, or male patient who is planning to father a child or donate sperm during study period.
9. Has evidence of any other coexisting disease or medical or psychological condition, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational product or could interfere with the interpretation of study results, or patient is at high risk for treatment complication in the opinion of the Investigator.
10. Vulnerable patients (e.g., employees of the clinical study center or any other individuals involved with the conduct of the study, or immediate family members of such individuals, persons kept in prison or other persons institutionalized by law enforcement).

Study Design:

This is a double-blind, randomized, active-controlled, parallel group, multicenter, Phase 3 study to evaluate the efficacy and safety of CT-P39 compared with Xolair, when subcutaneously administered as an add-on therapy for the treatment of patients with CSU who remain symptomatic despite an approved dose of nonsedating H_1-antihistamine treatment. All patients will continue to concomitantly receive an approved dose of nonsedating H_1-antihistamine treatment throughout the study.

Approximately 600 male and female patients with CSU, aged between 12 and 75 years (both inclusive), will be enrolled into the study and randomly assigned in a 2:2:1:1 ratio to receive one of the following: 300 mg of CT-P39, 300 mg of Xolair, 150 mg of CT-P39 or 150 mg of Xolair. This study will comprise 4 study periods (Screening Period, Treatment Period I, Treatment Period II, and Follow-up Period). The maximum duration of the study per patient will be 44 weeks: a Screening Period of 4 weeks, 2 Treatment Periods of 12 weeks each, and a Follow-up Period of 16 weeks.

<u>Screening Period (4 weeks)</u>

Screening evaluations will be completed within 28 days prior to the first study drug administration on Day 1 (Week 0). Patients' eligibility and baseline symptom scores will be assessed. Patients will start to receive an approved dose of protocol-defined nonsedating H_1-antihistamine at least 3 consecutive days immediately prior to start of patient eDiary record for baseline ISS7 (Day -7 to Day -1) in the Screening Period and continue taking the same dose throughout the study. Patients will be instructed to complete the patient eDiary twice daily (morning and evening) from Screening and throughout the study.

<u>Treatment Period I (12 weeks)</u>

On Day 1 (Week 0), approximately 600 patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomly assigned in a 2:2:1:1 ratio to one of the 4 treatment arms:

- Arm 1 (200 patients): 300 mg of CT-P39
- Arm 2 (200 patients): 300 mg of Xolair
- Arm 3 (100 patients): 150 mg of CT-P39
- Arm 4 (100 patients): 150 mg of Xolair

The patients will receive 3 doses of CT-P39 or Xolair as subcutaneous injections using a PFS every 4 weeks for

12 weeks. The randomization will be balanced by using permuted blocks and will be stratified by baseline ISS7 (< 13 points versus ≥ 13 points), body weight on Day 1 (< 80 kg versus ≥ 80 kg), and country. For patients who receive one (150 mg) injection of study drug, an additional 1 mL placebo injection using a PFS will be administered to maintain the study blind between the 2-dose levels (300 mg versus 150 mg). Efficacy, PK, QoL, safety, and immunogenicity data will be collected, and the primary endpoint will be measured prior to the study drug administration at Week 12.

Treatment Period II (12 weeks)

All patients who complete the Treatment Period I will undergo the second randomization process prior to the study drug administration at Week 12 and will enter the Treatment Period II to receive additional 3 doses of study drug every 4 weeks.

Patients will be stratified by decrease from baseline in ISS7 at Week 12 (≥ 5 points versus < 5 points) and body weight at Week 12 (< 80 kg versus ≥ 80 kg). During Treatment Period II, patients who are initially randomized to 300 mg of Xolair (Arm 2) in Treatment Period I, will be re-randomized in a ratio of 1:1 to switching arm (Arm 2-1) or non-switching arm (Arm 2-2). Patients assigned to switching arm (Arm 2-1) will undergo transition to 300 mg of CT-P39 and patients assigned to non-switching arm (Arm 2-2) will continue 300 mg of Xolair.

All patients who are initially randomly assigned to Arm 1 (300 mg of CT-P39) during Treatment Period I will continue to receive the same drug. All patients who are initially randomly assigned to Arm 3 (150 mg of CT-P39) or Arm 4 (150 mg of Xolair) during Treatment Period I, will continue to receive the same drug at an increased dose of 300 mg until end-of-treatment (EOT) visit.

All patients will receive 3 doses of either 300 mg of CT-P39 or 300 mg of Xolair every 4 weeks for 12 weeks during Treatment Period II. The last dose of study drug during the Treatment Period II will be given at Week 20 study visit and the EOT visit will be performed at Week 24.

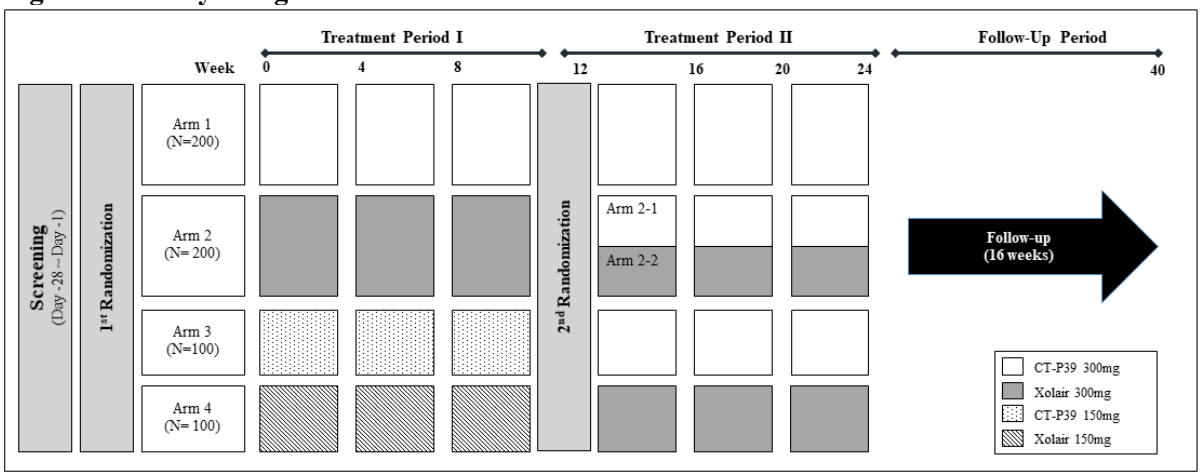
Patients who discontinue the study drug during any of treatment periods will also return to the study center by regular scheduled time intervals for planned clinical assessments including efficacy, QoL, PK, safety and immunogenicity.

Follow-up Period (16 weeks)

All patients will enter the Follow-up Period and be followed up for 16 weeks to assess additional efficacy, PK, QoL, safety, and immunogenicity data. Visits will be scheduled every 4 weeks and the end-of-study (EOS) visit will occur at Week 40. At the EOS visit, additional assessments including efficacy, QoL, PK, safety, and immunogenicity assessments will be performed.

During the Follow-up Period, no study drug will be given, and increasing the dose of the current nonsedating H_1-antihistamine treatment is not permitted. Patients may add one additional nonsedating H_1-antihistamine. Patients who discontinue the study drug during treatment periods may start adding one additional nonsedating H_1-antihistamine from the next regular visit of the last study drug administration visit. The goal of allowing additional H_1-antihistamine therapy during the Follow-up Period is to reduce patient dropout for further evaluation.

Figure S1. Study Design Overview



Week	0	4	8	12	16	20	24 (EOT)	28	32	36	40 (EOS)
Efficacy/Safety	→	→	→	→	→	→	→	→	→	→	→
PK	●	●	●	●	●	●	●				●
Immunogenicity	●	●	●	●	●	●	●				●
Quality of Life	●			●			●				●

Abbreviations: EOS = end-of-study; EOT = end-of-treatment; N = number of patients; PK = pharmacokinetics.

The study will be performed in a double-blind manner. To minimize the risk of unblinding, the study drug will be administered by unblinded study center personnel. The unblinded personnel who are responsible for administering study drugs will not be permitted to conduct any patient assessments.

Efficacy Assessments:

Data for efficacy assessments will be collected via patient eDiary. Patients will be instructed to complete the patient eDiary twice daily (morning and evening) from Screening until EOS visit. The data collected for 7 consecutive days (Day -7 to Day -1) prior to the Day 1 visit will be used as baseline data for weekly scores.

Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in ISS7 at Week 12. There will be co-primary evaluations of the primary endpoint to evaluate therapeutic equivalence and relative potency between CT-P39 and Xolair.

Secondary Efficacy Endpoints

- Change from baseline in ISS7 at Weeks 8 and 24
- Time to minimally important difference (MID; reduction of ≥ 5 points from baseline) response in ISS7 by Week 12
- Percentage of MID responders in ISS7 at Weeks 8, 12, and 24
- Change from baseline in UAS7 at Weeks 8, 12, and 24
- Percentage of patients with UAS7 of ≤ 6 points at Weeks 8, 12, and 24
- Percentage of complete responders (UAS7 = 0) in UAS7 at Weeks 8, 12, and 24
- Change from baseline in the weekly hives severity score at Weeks 8, 12, and 24
- Percentage of angioedema-free days from Weeks 4 to 12
- Change from baseline in number of tablets/week of rescue therapy at Week 8, 12, and 24

Pharmacokinetic Assessment:

The secondary PK endpoint is trough serum concentration (C_{trough}) of omalizumab.

Quality of Life Assessments:

- Change from baseline in the overall Dermatology Life Quality Index score at Weeks 12 and 24
- Change from baseline in the overall Chronic Urticaria Quality of Life Questionnaire score at Weeks 12 and 24

Safety Assessments:
Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs), serious adverse events (SAEs), AEs of special interest (AESIs: allergic reactions type I/anaphylaxis, injection site reactions, allergic reaction type III [serum sickness/serum sickness-like reaction], and parasitic [helminth] infections), immunogenicity including antidrug antibody and neutralizing antibody, total and free serum IgE, viral serology testing, C3, C4 and total hemolytic complement (CH_{50}) assessments, hypersensitivity monitoring (via vital sign and electrocardiogram [ECG] when indicated), physical examination, measurement of hematology, clinical chemistry, and urinalysis variables, measurement of vital signs, ECG, and body weight, pregnancy testing, and prior and concomitant medications.

Sample Size:
Sample size was derived based on a power analysis using PASS (Version 16.0, NCSS Statistical Software, LLC. Utah, United States). A total of 600 patients will be randomized in a 2:2:1:1 ratio to 300 mg of CT-P39 (Arm 1), 300 mg of Xolair (Arm 2), 150 mg of CT-P39 (Arm 3), or 150 mg of Xolair (Arm 4) treatment arms, respectively. For the demonstration of the therapeutic similarity between 300 mg of CT-P39 (Arm 1) and 300 mg of Xolair (Arm 2) in the mean change from baseline in ISS7 at Week 12, a sample size of 400 patients (200 patients per each arm) achieves approximately 95% statistical power based on the two one-sided 5% significance level and an equivalence margin of [− 2.5, + 2.0]. In the sample size calculation, the common standard deviation (SD) of the mean change from baseline in ISS7 at Week 12 is assumed to be 5.95 and the expected mean difference to be 0.
In order to support assay sensitivity and to evaluate the relative potency between CT-P39 and Xolair, additional 200 patients will be enrolled in 150 mg dose arms (100 patients in each of CT-P39 [Arm 3] and the Xolair [Arm 4] treatment arms). Using the observed mean and SD of change from baseline in ISS7 at Week 12 from ASTERIA I Study, which has the most similar study design to this study, a total sample size of 600 patients (200 patients for 150 mg dose arms and 400 patients for 300 mg dose arms) achieves an approximately 97% statistical power to demonstrate similarity using the relative potency of CT-P39 to the Xolair using a predefined margin of [0.5, 2.0].

Statistical Methods:
Data Analyses:
The study will be unblinded for the reporting purposes after database lock for data up to Week 24 for all patients. The unblinded team will be predefined and documented before performing the analyses. The study will remain blinded to the Investigators, patients, predefined blinded study center staffs and blinded teams in the Sponsor and [redacted] until the final clinical study report has been generated.
Statistical Analysis:
All statistical analyses will be conducted using Statistical Analysis System Software Version 9.4 or higher (SAS Institute Inc., Cary, North Carolina, United States). The statistical methods for this study will be described in a detailed Statistical Analysis Plan (SAP), which will be finalized before database lock. Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the clinical study report.
Full details of the statistical methods will be described in the SAP.
Continuous variables will be summarized by reporting the following descriptive statistics: the number of observations (n), mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency tables showing the number and percentage of patients within a particular category. Data will be listed in data listings.
Analysis Sets:
- Randomized Set: The randomized Set is defined as all randomly assigned patients prior to dosing on Day 1 regardless of whether they received any study drug (CT-P39 or Xolair).
- Modified intent-to-treat (mITT) Set: The mITT Set is defined as all randomly assigned patients who receive at least one full dose of either of the study drugs during the Treatment Period I. Patients will be analyzed to the arm they are randomized.
- Per-Protocol (PP) Set: The PP Set is defined as all randomly assigned patients who receive all 3 doses of study drug during the Treatment Period I and have an ISS7 assessment at Week 12. Patients with major protocol deviation that may affect the interpretation of study results of primary efficacy endpoint will be excluded from the PP Set. Final determinations of the PP Set will be made on case-by-case manner at the

blinded data review meeting.

- Pharmacokinetic Set: The PK Set is defined as all patients who receive at least one full dose of either of the study drugs during the Treatment Period I and have at least one post-treatment PK result prior to the dosing at Week 12. If any patients are found to be noncompliant with respect to dosing, a determination of the PK Set will be made on a case-by-case basis at the blinded data review meeting.
- Safety Set: The Safety Set is defined as all randomly assigned patients who receive at least one dose (full or partial) of study drug. Patients will be analyzed to the arm they are actually treated.

Efficacy Analysis:

Primary Endpoint:

The primary endpoint is the change from baseline in ISS7 at Week 12. There will be co-primary evaluations of the primary endpoint to evaluate therapeutic equivalence and relative potency between CT-P39 and Xolair.

The primary analyses will be performed using the mITT Set. If a patient has missing data of ISS7 at Week 12, the missing data will be imputed using multiple imputation. A supportive analysis will be repeated using the PP Set. To assess the robustness, a tipping point approach will be applied, where by the impact of missing data on the conclusions from the primary analysis of mean change from baseline will be assessed.

Comparison of the mean change from baseline in ISS7 of 300 mg arms at Week 12

Comparison of the mean change from baseline in ISS7 of CT-P39 300 mg treatment arm and Xolair 300 mg treatment arm at Week 12 will be analyzed using an analysis of covariance model with treatment as a fixed effect and baseline ISS7, body weight and country as covariates. Final determination of covariates and details will be described in the SAP. The difference of least squares means between 300 mg of CT-P39 (Arm 1) and 300 mg of Xolair (Arm 2) will be calculated based on aforesaid analysis of covariance model. Statistical equivalence will be declared if the two-sided 90% confidence interval (CI) of the difference falls entirely within an equivalence margin [− 2.5, + 2.0].

Relative potency

The relative potency of CT-P39 to the Xolair is defined as the dose of CT-P39 that produces the same biological response as one unit of the dose of the Xolair. The biological response will be estimated by the change from baseline in ISS7 at Week 12. Since the 2 treatments will be compared at the same 2-dose levels (300 mg and 150 mg), a 4-point assay will be used to calculate the relative potency and its CI. Statistical equivalence in terms of the relative potency will be declared if the two-sided 90% CI of the relative potency falls entirely within an equivalence margin [0.5, 2.0].

Secondary Endpoints:

All secondary efficacy endpoints will be analyzed using the mITT Set and PP Set. These will be summarized by treatment arms as appropriate and listed. In case of calculating parameters defining "responder and non-responder", the patient will be classified as a non-responder if a patient has missing weekly scores for the given week. Graphical presentations of data collected at each week may be presented, where applicable.

Safety Analysis:

Safety will be assessed through the summary of AEs (including SAEs), AESI, immunogenicity including antidrug antibody and neutralizing antibody, total and free serum IgE, hypersensitivity monitoring, vital signs, body weight, physical examination, clinical laboratory analyses, ECG, pregnancy testing, and prior and concomitant medications throughout the study. These summaries will be produced for the whole study and separately for the each Treatment Period where appropriate. Severity of AEs will be graded according to the Common Terminology Criteria for Adverse Events Version 5.0. All reported terms for AEs and medical history will be coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities. Prior and concomitant medication will be coded to drug class and preferred term using the World Health Organization drug dictionary. For AESIs, the incidence rate and its difference between treatment arms will be presented along with their 95% CI. All safety data including immunogenicity will be listed and summarized by treatment arm as appropriate in the Safety Set.

Pharmacokinetic Analysis:

Serum concentrations of omalizumab will be summarized using quantitative descriptive statistics (including geometric mean and coefficient of variation, as appropriate) by treatment arm and study visit. Pharmacokinetic parameter of C_{trough} will also be summarized using quantitative descriptive statistics (including geometric mean and coefficient of variation, as appropriate) by treatment and study visit. Graphical presentations of data may be added. All analyses will be performed using the PK Set.

Quality of Life Analysis:
Individual domain and overall Dermatology Life Quality Index score and Chronic Urticaria Quality of Life Questionnaire score will be summarized using descriptive statistics of actual value and change from baseline at scheduled visits for the mITT and PP Sets.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
CI	confidence interval
COVID 19	coronavirus disease 2019
CRO	contract research organization
CSR	clinical study report
CSU	chronic spontaneous urticaria
CTCAE	Common Terminology Criteria for Adverse Events
CU-Q_2oL	Chronic Urticaria Quality of Life Questionnaire
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EOS	end-of-study
EOT	end-of-treatment
EU	European Union
FcεRI	high-affinity IgE receptor for the Fc region of IgE
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HSS	hives severity score
HSS7	weekly hives severity score
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IP	Investigational product
ISS	itch severity score
ISS7	weekly itch severity score
IWRS	interactive web response system
LTRA	leukotriene receptor antagonist
MID	minimal important difference
mITT	modified intent-to-treat
PFS	prefilled syringe
PK	pharmacokinetics
PP	per-protocol
PVG	pharmacovigilance
QoL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System Software
SD	standard deviation

SmPC	summary of product characteristics
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
UAS	urticaria activity score
UAS7	weekly urticaria activity score
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information

DEFINITION OF TERMS

Study drug	CT-P39 or Xolair
Study treatment	CT-P39 or Xolair in combination with H_1-antihistamines

1 Introduction

1.1 Background

1.1.1 Chronic Spontaneous Urticaria

Urticaria is a common disease characterized by wheals and/or angioedema. While acute urticaria recovers completely within a week to a month, chronic urticaria persists for more than 6 weeks. Chronic spontaneous urticaria (CSU) is defined as chronic urticaria with no specific cause and accounts for two thirds of chronic urticaria cases (Roh 2019). Originally, the term CSU was interchangeable with chronic idiopathic urticaria, but currently, the term CSU is broader and includes patients with a known auto-antibody prior infection-related chronic urticaria who are now not considered 'idiopathic', as they do have a known trigger. In this new classification, CSU covers all noninducible chronic urticaria with chronic idiopathic urticaria (of unknown trigger) being a subset of it. However, this recent convention is not implanted in all countries yet, such as the United States (US). Nonetheless, the term of CSU will be used throughout this document for consistency following the international guideline, because CSU most accurately reflects the study population and intended use in the omalizumab clinical studies (Zuberbier *et al.,* 2018).

Chronic spontaneous urticaria is not a life-threatening disease but has a negative impact on the ability to perform daily activities and health-related quality of life (QoL). The number of patients with urticaria is increasing, up to 25% of the global population suffers from urticaria once in their lifetime. At any single time, 1.8% of the general population is suffering from CSU (Maurer *et al.,* 2011; Zuberbier *et al.,* 2010). Angioedema or deep tissue swelling occurs in approximately 40% of patients with CSU (Kaplan *et al.,* 2004; Maurer *et al.,* 2013).

Many symptoms of urticaria are the result of the actions of histamine on H_1 receptors. Thus, second generation H_1-antihistamines are the first-line standard treatment for CSU (Zuberbier *et al.,* 2018). However, only 44% of patients have reported a good response to H_1-antihistamine, 15% had partial improvement, and 17% had little or no benefit from taking H_1-antihistamine (Humphreys *et al.,* 1998). In case of patients continue to experience symptom despite receiving H_1-antihistamine at up 4 times higher than the approved dose (second-line), omalizumab, an anti-IgE antibody, is recommended as an add-on therapy to H_1-antihistamine (third-line; Zuberbier *et al.,* 2018).

1.1.2 Omalizumab

Omalizumab is a derived humanized monoclonal antibody, manufactured by recombinant deoxyribonucleic acid (DNA) technology in a Chinese hamster ovary mammalian cell line, and selectively binds to human IgE. By inhibiting the binding of IgE to the high-affinity IgE receptor for the Fc region of IgE (FcεRI), omalizumab reduces free IgE levels and reduction in surface-bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response.

Treatment with omalizumab also reduces the number of FcεRI receptors on basophils in atopic patients.

Omalizumab has been licensed for the treatment of moderate-to-severe allergic asthma in the US and for severe allergic asthma in Europe in adults and adolescents 12 years of age and older. It was approved for the treatment of CSU in adults and adolescents 12 years of age and older Europe and US afterwards. The mechanism by which these effects of omalizumab result in an improvement of CSU symptoms is unknown. Recently, omalizumab was also approved for the treatment of chronic rhinosinusitis with nasal polyps (Xolair United States Prescribing Information [USPI] 2021; Xolair Summary of Product Characteristics [SmPC] 2020).

1.2 CT-P39

CT-P39, containing the active ingredient omalizumab, is a recombinant humanized monoclonal antibody that is being developed and manufactured as a proposed biosimilar to Xolair (omalizumab) by the Sponsor. CT-P39 is identical to Xolair with respect to concentration, formulation, and presentation. The 150 mg of drug product (CT-P39) will have the same pharmaceutical form and strength as 150 mg Xolair (in a prefilled syringe [PFS] for subcutaneous injection) and is intended to have a similar quality profile compared with Xolair. The Sponsor plans to seek approval for all indications for which the innovator product has been approved by demonstrating similarity of CT-P39 with the reference product through an extensive array of quality, nonclinical, and clinical comparability assessments.

1.2.1 Nonclinical Studies

The nonclinical program for CT-P39 has been designed to support clinical studies and to demonstrate similarity in binding profiles and functional activities between CT-P39 and Xolair. CT-P39 was evaluated in nonclinical *in vitro* and *in vivo* studies in order to show comparability of the test article and Xolair. The *in vivo* study was conducted in accordance to Good Laboratory Practice standards.

Detailed information regarding the nonclinical pharmacology and toxicology of CT-P39 can be found in the Investigator's Brochure (IB).

1.2.2 Clinical Studies

The clinical data on Xolair has been published in scientific literature, regulatory submissions, and approved product information (Xolair USPI 2021; Xolair SmPC 2020). As CT-P39 is being developed as a proposed biosimilar to Xolair, the clinical findings for CT-P39 are expected to be in line with those of Xolair in terms of safety, pharmacokinetics (PK), and efficacy.

As part of the development program for CT-P39, two clinical studies were planned, and one of them has been completed.

Study CT-P39 1.1 was a Phase 1, randomized, double-blind, three-arm, parallel group, single-dose study to compare the PK and safety of CT-P39, European Union (EU)-approved Xolair, and US-licensed Xolair in healthy volunteers. The study showed the PK similarity following a single 150 mg injection of CT-P39, EU-approved Xolair, and US-licensed Xolair, and a CT-P39 was safe and well-tolerated in the healthy subjects.

The current Phase 3 study, CT-P39 3.1, is a randomized, double-blind, active-controlled, parallel group study to compare the efficacy, PK, QoL, safety, and immunogenicity of CT-P39 and Xolair after subcutaneous injections for 24 weeks (given once in every 4 weeks), in patients with CSU who remain symptomatic despite H_1-antihistamine treatment.

1.3 Study Rationale

CT-P39 is currently being developed by the Sponsor and is intended to be developed as a proposed biosimilar to Xolair. For a proposed biosimilar to be approved, it must be proven that there are no clinically meaningful differences between the two drug products. The stepwise 'totality of evidence' approach adopted by regulatory authorities for biosimilars means that the type of clinical studies needed varies on a case-by-case basis. However, statistically proven equivalence between proposed biosimilar and reference product in both PK and efficacy are usually required, as is a demonstration of acceptable safety and immunogenicity. Therefore, the PK profile of CT-P39, EU-approved Xolair, and US-licensed Xolair was compared to demonstrate PK equivalence in a Phase 1 study in healthy volunteers. An additional assessment of the similarity in efficacy, PK, QoL, safety, and immunogenicity will be carried out in this proposed comparative clinical study (CT-P39 3.1) in patients with CSU despite current use of H_1-antihistamines. The Sponsor considers that the proposed clinical development program will be sufficient to demonstrate PK equivalence (Study CT-P39 1.1 PK similarity healthy volunteer study), therapeutic equivalence and safety (Study CT-P39 3.1 comparative clinical similarity) of CT-P39 to the reference product.

The design of this study takes into account the EU Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies: Nonclinical and Clinical Issues (EMA 2012) and the Food and Drug Administration (FDA) Guideline on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (FDA 2015).

1.3.1 Rationale for Study Population

International regulations (WHO 2010; EMA 2012; FDA 2015; FDA 2020) suggest that proposed biosimilars should be tested in a population representative of the approved therapeutic indications of the reference product and sufficiently sensitive for detecting potential differences between the proposed biosimilar and the reference product.

Chronic spontaneous urticaria has been selected as indication for the comparative clinical study, due to the relatively high magnitude of the treatment effect observed in the Xolair clinical studies in this indication and approved standard doses (Casale *et al.,* 2015); thus, facilitating the detection of potential differences between CT-P39 and Xolair.

The study population in this study was selected in order to be representative of the original placebo-controlled studies supporting the development of the reference product and to align with the indications approved for the reference product.

1.3.2 Rationale for Dose Selection

In Treatment Period I, patients will receive either 150 mg or 300 mg of omalizumab as described in Section 3.1.

While the recommended dose in the EU and Japan for treatment of CSU is 300 mg every 4 weeks, both 150 mg and 300 mg every 4 weeks are approved in the US and Republic of Korea. The dose of 300 mg of omalizumab was approved and most commonly used since the maximum efficacy was reached at the drug exposure range corresponding to the 300 mg regimen, based on exposure-efficacy analyses. Additionally, 150 mg of omalizumab is approved in some countries since suboptimal efficacy was also reached at the dose of 150 mg (FDA 2014).

Therefore, the inclusion of the 150 mg CT-P39 and Xolair arms in the proposed therapeutic equivalence study will allow comparisons of 150 mg versus 300 mg treatment arms which has the potential to support the assay sensitivity and evaluation of relative potency between the 2 doses and assessments of relative potency between CT-P39 and Xolair, provided CT-P39 demonstrates similar dose-dependent treatment effects to the Xolair reference studies. In addition, it will allow comparisons of CT-P39 and Xolair at globally approved doses for CSU.

However, patients who received 150 mg of CT-P39 or Xolair during Treatment Period I will receive same drug with their dose increased to 300 mg during Treatment Period II in order to provide maximum efficacy.

1.4 Benefit and Risk Assessment

The CT-P39 will have the same pharmaceutical formulation and strength as Xolair (150 mg/mL). The proposed dosing regimen is in line with the approved labeling for Xolair (Xolair USPI 2021; Xolair SmPC 2020).

The proposed safety monitoring is deemed to be sufficient to monitor potential risks of CT-P39 administration. In view of the structural, biological, and toxicological similarity to Xolair, CT-P39 is expected to display a similar safety profile.

Based upon the clinical evidence as well as the proven safety profile of Xolair, the benefits of the conduct of the proposed clinical study outweigh the associated risks.

The benefit and risk assessments and the risk mitigation plans for coronavirus disease 2019 (COVID-19) are specified in Appendix 2. Risk assessments will be conducted during the study by the Sponsor through a sufficient discussion with the Investigators and data safety monitoring board (DSMB).

2 Study Objectives and Endpoints

2.1 Study Objectives

2.1.1 Primary Objectives

- To demonstrate the equivalence of CT-P39 to Xolair at a dose of 300 mg in terms of efficacy in patients with CSU as determined by change from baseline in weekly itch severity score (ISS7) at Week 12
- To evaluate the relative potency of CT-P39 compared with Xolair as determined by change from baseline in ISS7 at Week 12

2.1.2 Secondary Objectives

- To evaluate dose response in terms of efficacy between 300 mg and 150 mg for CT-P39 and Xolair
- To evaluate additional efficacy of CT-P39 and Xolair at each dose level of 300 mg and 150 mg
- To evaluate the PK, QoL, safety, and immunogenicity of CT-P39 and Xolair

2.2 Study Endpoints

2.2.1 Primary Endpoint

The primary efficacy endpoint is the change from baseline in ISS7 at Week 12. There will be co-primary evaluations of the primary endpoint to evaluate therapeutic equivalence and relative potency between CT-P39 and Xolair.

2.2.2 Secondary Endpoints

2.2.2.1 Efficacy Endpoints

The secondary efficacy endpoints will be the following:

- Change from baseline in ISS7 at Weeks 8 and 24
- Time to minimal important difference (MID; reduction of ≥ 5 points from baseline) response in ISS7 by Week 12
- Percentage of MID responders in ISS7 at Weeks 8, 12, and 24
- Change from baseline in weekly urticaria activity score (UAS7) at Weeks 8, 12, and 24
- Percentage of patients with UAS7 of ≤ 6 points at Weeks 8, 12, and 24

- Percentage of complete responders (UAS7 = 0) in UAS7 at Weeks 8, 12, and 24
- Change from baseline in the weekly hives severity scores (HSS7) at Weeks 8, 12, and 24
- Percentage of angioedema-free days from Weeks 4 to 12
- Change from baseline in number of tablets/week of rescue therapy at Week 8, 12, and 24

2.2.2.2 Pharmacokinetic Endpoint

The secondary PK endpoint is trough serum concentration (C_{trough}) of omalizumab.

2.2.2.3 Quality of Life Endpoints

The secondary QoL endpoints will be the following:

- Change from baseline in the overall Dermatology Life Quality Index (DLQI) score at Weeks 12 and 24
- Change from baseline in the overall Chronic Urticaria Quality of Life Questionnaire (CU-Q_2oL) score at Weeks 12 and 24

2.2.2.4 Safety Endpoints

The secondary safety endpoints will be following:

- Incidence and severity of adverse events (AEs), including serious adverse events (SAEs)
- Incidence and severity of adverse events of special interest (AESIs)
- Immunogenicity, as assessed by the incidence of antidrug antibody and neutralizing antibody
- Total and free serum IgE
- Hypersensitivity monitoring
- Vital sign assessments
- Physical examination findings
- Clinical laboratory analyses
- Electrocardiogram (ECG)
- Body weight
- Pregnancy testing
- Prior and concomitant medications

3 Investigational Plan

3.1 Study Design

This is a double-blind, randomized, active-controlled, parallel group, multicenter, Phase 3 study to evaluate the efficacy and safety of CT-P39 compared with Xolair, when subcutaneously administered as an add-on therapy for the treatment of patients with CSU who remain symptomatic despite an approved dose of nonsedating H_1-antihistamine treatment. All patients will continue to concomitantly receive an approved dose of nonsedating H_1-antihistamine treatment throughout the study.

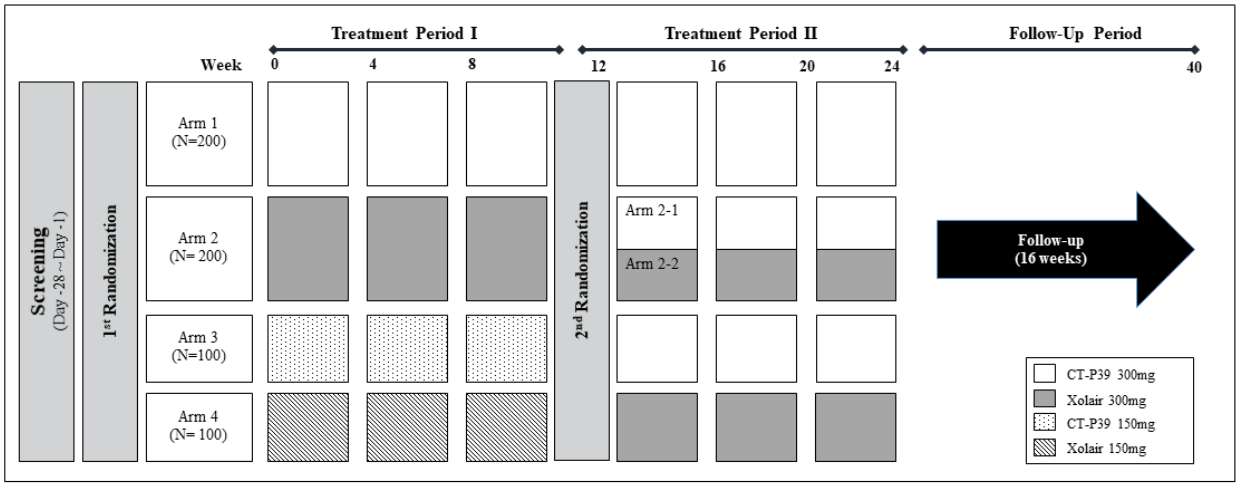
Approximately 600 male and female patients with CSU, aged between 12 and 75 years (both inclusive), will be enrolled into the study and randomly assigned in a 2:2:1:1 ratio to receive one of the following: 300 mg of CT-P39, 300 mg of Xolair, 150 mg of CT-P39, or 150 mg of Xolair. This study will comprise of 4 study periods (Screening Period, Treatment Period I, Treatment Period II, and Follow-up Period). The maximum duration of the study per patient will be 44 weeks: a Screening Period of 4 weeks, 2 Treatment Periods of 12 weeks each, and a Follow-up Period of 16 weeks.

The study will be performed in a double-blind manner. To minimize the risk of unblinding, the study drug will be administered by unblinded study center personnel. The unblinded personnel who are responsible for administering study drugs will not be permitted to conduct any patient assessments.

Details of each visit and assessment that will be performed at each time point is specified in the schedule of assessments (Appendix 1).

The study design and patient assessment overview are presented in Figure 3-1.

Figure 3-1 Study Design Overview



Week	0	4	8	12	16	20	24 (EOT)	28	32	36	40 (EOS)
Efficacy/Safety	→	→	→	→	→	→	→	→	→	→	→
PK	●	●	●	●	●	●	●				●
Immunogenicity	●	●	●	●	●	●	●				●
Quality of Life	●			●			●				●

Abbreviations: EOS = end-of-study; EOT = end-of-treatment; N = number of patients; PK = pharmacokinetics.

Screening Period (4 weeks)

Screening evaluations will be completed within 28 days prior to the first study drug administration on Day 1 (Week 0). Patients' eligibility and baseline symptom scores will be assessed. Patients will start to receive an approved dose of protocol-defined nonsedating H_1-antihistamine (Section 5.4.2) at least 3 consecutive days immediately prior to the start of patient electronic diary (eDiary) record for baseline ISS7 (Day -7 to Day -1) in the Screening Period and continue taking the same dose throughout the study. Patients will be instructed to complete the patient eDiary twice daily (morning and evening) from Screening and throughout the study.

Treatment Period I (12 weeks)

On Day 1 (Week 0), approximately 600 patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomly assigned in a 2:2:1:1 ratio to one of the 4 treatment arms:

- Arm 1 (200 patients): 300 mg of CT-P39
- Arm 2 (200 patients): 300 mg of Xolair
- Arm 3 (100 patients): 150 mg of CT-P39

- Arm 4 (100 patients): 150 mg of Xolair

The patients will receive 3 doses of CT-P39 or Xolair as subcutaneous injections using a PFS every 4 weeks for 12 weeks. The randomization will be balanced by using permuted blocks and will be stratified by baseline ISS7 (< 13 points versus ≥ 13 points), body weight on Day 1 (< 80 kg versus ≥ 80 kg) and country. For patients who receive one (150 mg) injection of study drug, an additional 1 mL placebo injection using a PFS will be administered to maintain the study blind between the 2-dose levels (300 mg versus 150 mg). Efficacy, PK, QoL, safety, and immunogenicity data will be collected, and the primary endpoint will be measured prior to the study drug administration at Week 12.

Treatment Period II (12 weeks)

All patients who complete the Treatment Period I will undergo the second randomization process prior to the study drug administration at Week 12 and will enter the Treatment Period II to receive additional 3 doses of study drug every 4 weeks.

Patients will be stratified by decrease from baseline in ISS7 at Week 12 (≥ 5 points versus < 5 points) and body weight at Week 12 (< 80 kg versus ≥ 80 kg). During Treatment Period II, patients who are initially randomized to 300 mg of Xolair (Arm 2) in Treatment Period I, will be re-randomized in a ratio of 1:1 to switching arm (Arm 2-1) or non-switching arm (Arm 2-2). Patients assigned to switching arm (Arm 2-1) will undergo transition to 300 mg of CT-P39 and patients assigned to non-switching arm (Arm 2-2) will continue 300 mg of Xolair.

All patients who are initially randomly assigned to Arm 1 (300 mg of CT-P39) during Treatment Period I will continue to receive the same drug. All patients who are initially randomly assigned to Arm 3 (150 mg of CT-P39) or Arm 4 (150 mg of Xolair) during Treatment Period I, will continue to receive the same drug at an increased dose of 300 mg until the end-of-treatment (EOT) visit.

All patients will receive 3 doses of either 300 mg of CT-P39 or 300 mg of Xolair every 4 weeks for 12 weeks during Treatment Period II. The last dose of study drug during the Treatment Period II will be given at Week 20 study visit and the EOT visit will be performed at Week 24.

Patients who discontinue the study drug during any of treatment periods will also return to the study center by regular scheduled time intervals for planned clinical assessments including efficacy, QoL, PK, safety, and immunogenicity.

Follow-up Period (16 weeks)

All patients will enter the Follow-up Period and be followed up for 16 weeks to assess additional efficacy and safety data. Visits will be scheduled every 4 weeks and the end-of-study (EOS) visit will occur at Week 40. At the EOS visit, additional assessments including efficacy, QoL, PK, safety, and immunogenicity assessments will be performed.

During the Follow-up Period, no study drug will be given, and increasing the dose of the current nonsedating H_1-antihistamine treatment is not permitted. Patients may add one additional nonsedating H_1-antihistamine listed in Section 5.4.2. Patients who discontinue the study drug during treatment periods may start adding one additional nonsedating H_1-antihistamine from the next regular visit of the last study drug administration visit. The goal of allowing additional H_1-antihistamine therapy during the Follow-up Period is to reduce patient dropout for further evaluation.

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

It is expected that approximately 600 patients will be enrolled at approximately 65 study centers in 7 countries. Male or female patients with a history of at least 6 months of CSU who had hives and itching for 6 consecutive weeks or more despite current use of H_1-antihistamines for this time period will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

4.1.1 Inclusion Criteria

Each patient must meet all of the following criteria to be randomized in this study:

1. Male or female between 12 and 75 years of age (both inclusive; age limits would depend on country-specific regulation).

2. Have been diagnosed with CSU for at least 6 months prior to the first study drug administration.

3. Must be diagnosed as CSU refractory to H_1-antihistamine defined as below:

    a) Presence of hives associated with itching for ≥ 6 consecutive weeks at any time prior to the first study drug administration despite current use of H_1-antihistamine treatment for this time period

    b) Weekly itch severity score (range 0 to 21 points) ≥ 8 points and UAS7 (range 0 to 42 points) ≥ 16 points in the 7 consecutive days (Day -7 to Day -1) prior to the first study drug administration

    c) Documented use of an approved dosage of nonsedating H_1-antihistamine for CSU for at least 3 consecutive days immediately prior to the start of patient eDiary record for baseline ISS7 (Day -7 to Day -1)

4. Has patient eDiary entries without missing data in the 7 consecutive days (Day -7 to Day -1) prior to the first study drug administration.

5. Be willing and able to complete a patient eDiary twice daily (morning and evening) throughout the study.

6. Patient and/or their legally authorized representative are informed and will be given ample time and opportunity to read and/or understand the nature and purpose of this study including possible risks and side effects and must sign the informed consent form (ICF) before any specific procedures.

7. Female patient must agree to use highly effective methods of contraception consistent with local regulations throughout the study period (excluding women who are not of childbearing potential). Examples include the following:

    a) Combined (estrogen and progestogen containing) or progestogen-only hormonal contraceptives associated with inhibition of ovulation

    b) Intrauterine device or intrauterine hormone-releasing system

    c) True abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to investigational drug, and withdrawal are not acceptable methods of contraception.

Menopausal female patients must have experienced their last period more than 1 year prior to the date of informed consent to be classified as not of childbearing potential. Male patient who is sexually active with a woman of childbearing potential must agree to use highly effective method described as above or two acceptable methods of contraception (e.g., male or female condom AND additional hormonal or barrier contraceptive method other than condom by female partner) consistent with local regulations throughout the study period. Contraception is not required if either patient or his/her partner who has been surgically sterilized more than 24 weeks prior to the date of informed consent.

4.1.2 Exclusion Criteria

A patient meeting any of the following criteria will be excluded from the study:

1. Has a chronic urticaria with clearly defined underlying etiology (e.g., physical urticaria such as acute, solar, cholinergic, heat, cold, aquagenic, pressure or contact) other than CSU or any disease with symptoms of urticaria or angioedema (e.g., urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary or acquired angioedema, lymphoma, leukemia or generalized cancer).

2. Has a body weight of < 30 kg.

3. Has a medical history of and/or current disease including any of the following:

   a) History of clinically significant allergic reaction and/or hypersensitivity to any component of omalizumab, Chinese hamster ovary cell products, other recombinant human or humanized antibodies, H_1-antihistamines, or dry natural rubber (a derivative of latex)

   b) History of and/or concomitant myocardial infarction

   c) History of anaphylactic shock

   d) History of and/or concomitant immune complex disease (including allergic reaction type III), hyperimmunoglobulin E syndrome, autoimmune disease, or bronchopulmonary aspergillosis

   e) Any active skin disease associated with itch including atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, or senile pruritus

   f) A known infection with human immunodeficiency virus (HIV), hepatitis B, hepatitis C, or any active infection requiring treatment, except adequately treated and completely recovered past infections

   g) Any active malignancy or history of malignancy except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ

4. Has history of and/or a current use of medications including any of the following:

   a) Treatment with omalizumab or other monoclonal antibodies, protein, fusion protein, or other biologic agent targeting IgE

   b) Treatment with an investigational drug within 4 weeks or 5 half-lives (whichever is longer) prior to the first study drug administration

   c) Routine administration (i.e., daily or every other day for ≥ 5 consecutive days) of systemic glucocorticoids, hydroxychloroquine, methotrexate, cyclosporine, azathioprine, cyclophosphamide, tacrolimus, or mycophenolate mofetil within 5 weeks prior to the first study drug administration

   d) Intravenous immunoglobulin G or plasmapheresis within 5 weeks prior to the first study drug administration

e) Regular (i.e., daily or every other day for ≥ 5 consecutive days) use of oral doxepin within 3 weeks prior to the first study drug administration

f) Use of any H_2-antihistamine or leukotriene receptor antagonist (LTRA) within 2 weeks prior to the first study drug administration (However, continuing H_2-antihistamine or LTRA treatment for disease other than CSU is allowed)

g) Use of beta-blocker therapy within 2 weeks prior to the first study drug administration

h) Use of H_1-antihistamines at greater than approved doses from 3 days prior to the start of patient eDiary record for baseline ISS7 (Day -7 to Day -1)

5. Diagnosed with parasitic diseases or colonization on stool evaluation for ova and parasites (stool ova and parasite examination should be performed in patients who meet both the following criteria):

   a) Correspond to any of risk factors for parasitic disease

      - Travel within 6 months prior to the first study drug administration or living in an endemic area of parasitic infections
      - Chronic gastrointestinal symptoms
      - Chronic immunosuppression

   b) Absolute eosinophil count > 2 × upper limit of normal (ULN)

6. Unable to receive background therapy and rescue therapy with protocol-defined H_1-antihistamines or contraindicated to epinephrine or other components of these agents as per Investigator's discretion.

7. Has ongoing or a history of alcohol or drug abuse within 6 months prior to the first study drug administration.

8. Female patient who is currently pregnant or breastfeeding, or plans to become pregnant or breastfeed, or male patient who is planning to father a child or donate sperm during study period.

9. Has evidence of any other coexisting disease or medical or psychological condition, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable

suspicion of a disease or condition that contraindicates the use of an investigational product (IP) or could interfere with the interpretation of study results, or patient is at high risk for treatment complication in the opinion of the Investigator.

10. Vulnerable patients (e.g., employees of the clinical study center or any other individuals involved with the conduct of the study, or immediate family members of such individuals, persons kept in prison or other persons institutionalized by law enforcement).

4.2 Withdrawal of Patients from the Study

Patients are free to discontinue from the study treatment or withdraw from the study at any time for any reason. The Investigator may also discontinue the study treatment at any time in the interest of patient safety.

The primary reason for the discontinuation of the study treatment and study termination must be recorded in the patient's medical record and in the electronic case report form (eCRF) with any comments (spontaneous or elicited) or complaints made by the patient, date of cessation of study treatment and the total amount of study treatment administered.

The study treatment can be discontinued due to any of the following reasons:

- Patient refuses to continue study drug administration
- Patient develops signs of disease progression in the judgment of the Investigator
- Patient has any AE that would compromise his or her safety if he or she continues to receive the study drug
- Patient has a significant protocol deviation(s)
- Patient becomes pregnant
- Investigator's decision

As it is vital to obtain follow-up data, the patients who discontinue the study drug during any of treatment periods will visit the study center by regular scheduled time intervals until Week 40 for planned clinical assessments including efficacy, QoL, PK, safety and immunogenicity.

A patient can be discontinued from the study and study treatment due to any of the following:

- Patient withdraws consent or refuses to continue procedures/observations

- Patient is lost to follow-up (patient did not visit the study center and all attempts to contact failed)
- Patient has an AE for which he or she cannot continue to participate in this study
- Investigator's decision
- Study is terminated by the Sponsor

If a patient withdraws from the study, the last visit will be considered as the EOS visit and the all assessments planned for the EOS visit should be performed. Otherwise, a patient will be required to attend for the regularly scheduled EOS visit.

When possible, the Sponsor should be notified of the study treatment discontinuation and withdrawal of a patient from the study. If necessary, the Investigator may discuss with the Sponsor or its designee any patient's reason for treatment discontinuation or withdrawal from the study. The Sponsor may be contacted if clarification is required on a case-by-case basis. All patients who are terminated from the study will retain their patient identification number.

4.2.1 Replacement of Patients

Patients who receive study drug and discontinue before the study completion will not be replaced. Patients who failed Screening, for any reason, can be rescreened only once. If there is unusual situation that justifies consideration for additional rescreening, the Investigator is recommended to discuss with the Sponsor. Rescreened patient will be assigned with new patient identification number.

4.3 Premature Termination of the Study

The Sponsor reserves the right to terminate the study at any time for reasonable medical and/or administrative reasons. As far as possible, this should occur after mutual consultation.

If the study is terminated prematurely by the Sponsor, all patients will be kept fully informed and an appropriate follow-up examination of the patients will be arranged. The Investigator will inform the Independent Ethics Committee (IEC; or Institutional Review Board, where applicable) of any premature termination or suspension of the study.

5 Study Treatment

5.1 Method of Assigning Patients to Treatment Groups

An interactive web response system (IWRS) will be used for the randomization. Unblinded biostatisticians will generate the randomization schedule for IWRS, which will link sequential patient randomization numbers to treatment codes.

Randomization for Treatment Period I (first randomization)

During the Treatment Period I, the randomization will be stratified by:

- Baseline ISS7 (< 13 points versus ≥ 13 points)
- Body weight on Day 1 (< 80 kg versus ≥ 80 kg)
- Country

Re-randomization for Treatment Period II (second randomization)

During the Treatment Period II, the randomization will be stratified by:

- Decrease from baseline in ISS7 at Week 12 (< 5 points versus ≥ 5 points)
- Body weight at Week 12 (< 80 kg versus ≥ 80 kg)

The second randomization process will be conducted in all treatment arms to maintain the study blind. The details of stratification factors will be described in the randomization specification document, which will be provided as a separate document. If patient's ISS7 at Week 12 is missing, decrease from baseline in ISS7 at the last observed time point will be used for stratification.

5.2 Identity of Investigational Products

CT-P39 is a monoclonal antibody which is being developed by the Sponsor as a proposed biosimilar to Xolair. The company code of the product is CT-P39.

The International Nonproprietary Name of the commercially available reference material (Xolair) is omalizumab and the Chemical Abstract Service number of omalizumab is 242138-07-4. The chemical name of omalizumab is recombinant humanized monoclonal antibody to IgE. In this study, EU-approved Xolair will be used as reference drug.

Xolair is administered as subcutaneous injection using a PFS. Each PFS of Xolair contains sterile, preservative-free, clear to slightly opalescent and colorless to pale brownish-yellow solution for

subcutaneous injection. Each PFS delivers 150 mg omalizumab in 1 mL and contains L-arginine hydrochloride (42.1 mg), L-histidine (1.37 mg), L-histidine hydrochloride monohydrate (2.34 mg), and polysorbate 20 (0.4 mg).

CT-P39 is administered as a subcutaneous injection using a PFS. Each PFS of CT-P39 contains a sterile, preservative-free, clear to opalescent and colorless to pale brownish-yellow solution for subcutaneous injection. Each PFS delivers 150 mg omalizumab in 1 mL and contains L-arginine hydrochloride (42.1 mg), L-histidine (1.37 mg), L-histidine hydrochloride monohydrate (2.34 mg), and polysorbate 20 (0.4 mg). The composition of CT-P39 150 mg is identical to that of Xolair. For further details, see the IB.

5.3 Identity of Placebo Product

During the Treatment Period I, an additional 1 mL placebo solution using a PFS will be administered to patients who are randomly assigned to receive 150 mg of CT-P39 or 150 mg of Xolair to maintain the study blind between the 2-dose levels (150 mg and 300 mg).

The placebo contains the same ingredients as the Xolair formulation listed above, excluding omalizumab. Each placebo PFS contains L-arginine hydrochloride (42.1 mg), L-histidine (1.37 mg), L-histidine hydrochloride monohydrate (2.34 mg), and polysorbate 20 (0.4 mg) in 1 mL.

Because placebo does not contain omalizumab, it is colorless and transparent, unlike Xolair or CT-P39, which is very pale brownish-yellow. To prevent possible unblinding risk, the detail plans are specified in Section 5.8.

5.4 Treatment Administered

5.4.1 CT-P39 and Xolair

During the Treatment Period I, patients will receive 300 mg or 150 mg of CT-P39 or Xolair subcutaneously using a PFS every 4 weeks for 12 weeks (total 3 doses, 1 each given on Weeks 0, 4, and 8) as per the first randomization. Patients will remain in study center for 2 hours after study drug administration for anaphylaxis observation.

During the Treatment Period II, patients will receive 300 mg of CT-P39 or Xolair subcutaneously using a PFS every 4 weeks for 12 weeks (total 3 doses, 1 each given on Weeks 12, 16, and 20) as per the second randomization. Patients will remain in study center for an hour after study drug administration for anaphylaxis observation.

Study drug will be administered at the fixed visit schedule with visit window of + 3 days for Week 12 visit and visit window of ± 3 days for rest of visits (Appendix 1). Study drug should be administered preferably within 1 week from the planned dosing date. If dose delay of more than 1 week or missed dose is expected, it should be discussed with Sponsor or its designee regarding the patient's eligibility to continue study treatment.

Each patient will receive 2 subcutaneous injections per dosing day using a PFS during Treatment Periods I and II. For patients who receive one (150 mg) injection of study drug, an additional 1 mL placebo solution using a PFS will be administered to maintain the study blind between the 2-dose levels (300 mg and 150 mg).

The study drug will be administered subcutaneously to patients in the deltoid region of the right or left arm. Alternatively, the injections can be administered in the thigh if medically significant reasons preclude administration in the deltoid region. The second injection will be administered at injection site other than the first injection, at least 2.5 cm (or 1 inch) from the area used earlier.

The study drug will be handled and administered by delegated unblinded study staff. Patients will be blinded through the use of a blindfold, screen or similar method during the dosing procedure so that the injection syringe will not be visible to the patient. The details regarding blinding is described in Section 5.8.

5.4.2 Nonsedating H_1-Antihistamines

All patients will be allowed to take one of the predefined nonsedating H_1-antihistamines at approved dose throughout the study. The nonsedating H_1-antihistamines and doses allowed during the study are as following (the drug and dose in the following list will be used in line with local approval status):

- Bilastine 20 mg once daily
- Cetirizine 5 or 10 mg once daily
- Desloratadine 5 mg once daily
- Fexofenadine 60 mg twice daily or 180 mg once daily
- Levocetirizine dihydrochloride 2.5 or 5 mg once daily
- Loratadine 10 mg once daily
- Rupatadine 10 mg once daily

Patients will start to take approved dose of H_1-antihistamine for CSU at least 3 consecutive days immediately prior to the start of patient eDiary record for baseline ISS7 (Day -7 to Day -1) in the Screening Period and maintain the stable nonsedating H_1-antihistamine treatment regimen throughout the study. Increasing the dose of the nonsedating H_1-antihistamine treatment is not permitted throughout the study. Patients are permitted to add one additional H_1-antihistamine therapy only during the Follow-up Period. If a patient who discontinues the study drug during treatment periods, it is permitted to start adding one additional nonsedating H_1-antihistamine from the next regular visit of the last study drug administration visit.

5.5 Prior, Concomitant and Subsequent Therapy

Information (e.g., drug name, date[s] of administration, etc.) about prior medications taken by the patient within 30 days prior to the first study drug administration (inclusive of the applicable periods for prohibited medications as defined in Section 5.6) will be recorded in both the source documents and eCRF.

All patients should take protocol-defined nonsedating H_1-antihistamine medications at approved doses from at least 3 consecutive days immediately prior to start of patient eDiary record for baseline ISS7 (Day -7 to Day -1) in the Screening Period until the EOS visit. Patients will be allowed to take one additional nonsedating H_1-anithistamine as described in Section 5.4.2.

Patients taking either H_2-antihistamines or LTRAs for diseases other than CSU (e.g., asthma or gastroesophageal reflux disease) will be permitted to continue their use only when they maintain the dose of LTRA and/or H_2-antihistamines during the study. These diseases and the drug use must be recorded as part of the medical history and prior medication collected during the Screening Period. Inhaled asthma controllers, including corticosteroids, are also permitted during the study.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the Investigator. All concomitant medications should be reported to the Investigator and recorded on the appropriate eCRF and source document. Any changes in concomitant medications also will be recorded in the patient's eCRF and source documents. All concomitant medications used during the study will be recorded until the EOS visit.

Use of all prior and concomitant medications for the treatment of CSU, from the diagnosis of disease until the EOS visit, will be recorded in the patient's eCRF and source documents.

It is the Investigator's responsibility to ensure that details regarding the medication are adequately recorded in both the source documents and eCRF.

5.5.1 Rescue Therapy

For the duration of the study, nonsedating H_1-antihistamine, in addition to being used as background medication, will be allowed as rescue therapy for itch relief on an as-needed basis (dose specified in Section 5.4.2) throughout the study. The selection of the rescue medication should be made once for an individual patient. A switch of the rescue medication for an individual patient is not permitted. The information about the rescue therapy use will be reported on the patient eDiary daily.

5.5.2 Epinephrine

During the study, patients may be supplied with epinephrine auto-injector (or local standard of care, in case of epinephrine auto-injector is not available) for treatment of anaphylactic reactions at the Investigator's discretion. Patients will be trained on how to detect such reactions and how to use epinephrine. After any use of epinephrine, patients will need to seek immediate medical attention to ensure that the initial reaction has been successfully controlled and/or to trigger additional therapeutic steps. The use of epinephrine will be recorded on source document and the eCRF page.

5.6 Prohibited Therapy

The following medications, treatments or procedures are prohibited during the study. Patients who have received or plan to receive these prohibited medications or treatments will not be enrolled in the study (Section 4.1.2). Patients who receive any prohibited therapy during the Screening Period should be considered a screen failure. Intake of any of the following prohibited therapy by the patients after randomization will be considered as protocol deviation.

- Omalizumab other than study drug or any other monoclonal antibodies, protein, fusion protein, or other biologic agent targeting IgE
- Any other investigational drugs from 4 weeks or 5 half-lives (whichever is longer) prior to the first study drug administration
- Routine administration (i.e., daily or every other day for ≥ 5 consecutive days) of systemic glucocorticoids, hydroxychloroquine, methotrexate, cyclosporine, azathioprine, cyclophosphamide, tacrolimus, or mycophenolate mofetil from 5 weeks prior to the first study drug administration
- Intravenous immunoglobulin G or plasmapheresis from 5 weeks prior to the first study drug administration

- Regular (i.e., daily or every other day for ≥ 5 consecutive days) use of oral doxepin from 3 weeks prior to first study administration
- Use of any H_2-antihistamine or LTRA from 2 weeks prior to the first study administration
  Note: Patients taking either H_2-antihistamines or LTRAs for diseases other than CSU (e.g., asthma or gastroesophageal reflux disease) will be permitted to continue their use only when they maintain the dose of H_2-antihistamines and/or LTRA during the study.
- Use of beta-blocker therapy from 2 weeks prior to the first study drug administration
- Use of any H_1-antihistamines at greater than approved doses from 3 days prior to the start of patient eDiary record for baseline ISS7 (Day -7 to Day -1) in the Screening Period

5.7 Management of Clinical Supplies

5.7.1 Study Drug Package, Labeling, and Storage

The appropriate number of PFS of study drug will be allocated to each patient via the IWRS at each visit.

A label will be attached to the outside of each patient kit, as well as to the immediate container. The text will be compliant with local regulatory requirements and may include some of the following information:

- Protocol number
- Patient number/site number
- Contents and quantity
- Lot number
- Randomization code/kit number
- Investigator's name
- Route of administration
- Directions for use
- Storage instructions
- Caution statement (for clinical study use only)
- Sponsor's contact name and address
- Expiry date

All study drug supplies must be stored in a secured area with limited access and in accordance with the manufacturer's instructions. They will be stored in a refrigerator at from 2.0°C to 8.0°C (36.0°F to 46.0°F) and will not be frozen. The immediate containers must be kept in the outer carton until use to protect the study drug from light. The recommended storage conditions, and expiry date where required, are stated in the product label approved by each regulatory authority.

5.7.2 Study Drug Accountability

It is the responsibility of the clinical Investigator to ensure that all study drug received at the study center will be inventoried and accounted for throughout the study and the result recorded in the drug accountability form will be maintained at the study center. The study drug accountability will be verified by the monitor during on-site monitoring visits. Study drug will be stored in a limited access area under appropriate environmental conditions.

The Investigator agrees not to supply the study drug to any person other than Sub-Investigators, designated staff, and the patients participating in the study. Study drug may not be relabeled or reassigned for use by other patients unless approved by the Sponsor.

The used syringes can only be destroyed if it is according to local standard operating procedures (SOP) and a specific authorization is given by the Sponsor. Permission will be granted by the Sponsor on a study-center-by-study-center basis after reviewing the study center destruction policy. This authorization may also be granted to destroy used syringes immediately after administering the study drug to patients. The list of destroyed syringes must be recorded. The Investigator agrees to neither dispense the study drug from, nor store it at, any study center other than the study centers agreed upon with the Sponsor.

See the pharmacy manual for details of the study drug accountability and destruction.

5.8 Blinding

This study will be double-blind until the end of the study. The randomization codes will not be revealed to study patients, Investigators, and study center personnel, except for delegated unblinded staff who will handle the study drug and predefined unblinded teams in the Sponsor and contract research organization (CRO) until the final clinical study report (CSR) has been generated.

As the presentation of the study drugs and placebo are not identical in visual appearance, the trained clinical staff member(s) responsible for drug administration (e.g., nurse/physician, etc.) will be designated as unblinded study center personnel and will not be involved in any clinical or safety evaluations that are part of the blinded protocol or have other patient contact. Patients will

be blinded through the use of a blindfold, screen or similar method during the dosing procedure so that the injection syringe will not be visible to patient. Blinded staff will be absent during injection and remain blinded throughout the study.

5.8.1 Breaking the Blind

Under normal circumstances, the blind should not be broken. The blind should be broken only if specific emergency treatment would be dictated as knowing the study drug assignment is required for medical management. In such cases, the Investigator may, in an emergency, determine the identity of the study drug by using the applicable procedure in the IWRS (see study manual, which is provided as a separate document).

The date, time and reason for the unblinding must be documented in source document and the appropriate field of the eCRF and the medical monitor will be informed as soon as possible. All calls resulting in an unblinding event will be recorded and reported by the IWRS to the medical monitor and the Sponsor. In cases where there are ethical reasons for the patient to remain in the study, the Investigator must obtain specific approval from the Sponsor or its designee for the patient to continue in the study.

[redacted] pharmacovigilance (PVG) will have access to the randomization code, if suspected unexpected serious adverse reactions (SUSARs), which are subject to expedited reporting, should be unblinded before submission to the regulatory authorities.

The DSMB and the statistical team who provide the safety analyses for the DSMB will also be unblinded in the upon request from DSMB members during closed session.

The overall randomization code will be broken only for reporting purposes. This will occur after database lock for data up to Week 24 for all patients. The unblinded personnel will be predefined and documented before performing the analyses. The study will remain blinded to the Investigators, patients, predefined blinded study center staffs, and blinded teams in the Sponsor and [redacted] until the final CSR has been generated.

5.9 Treatment Compliance

Patient compliance will be determined based on drug accountability as well as source documents.

Every effort will be made to encourage patients' compliance with the study visits. A dosing visit window of + 3 days is allowed for Week 12 visit and visit window of ± 3 days is allowed for rest of visits. The date and time of the study drug administration will be documented. Administration

of co-administered treatments (i.e., nonsedating H_1-antihistamines) will be recorded throughout the study.

6 Study Assessments and Procedures

6.1 Efficacy Assessments

6.1.1 Patient eDiary

Data for efficacy assessments will be collected via patient eDiary. The patient eDiary is a mobile device application software. The patient eDiary will be installed in patient's own smartphone device at the first Screening visit. Patients will be instructed to complete the patient eDiary twice daily (morning and evening) from Screening until EOS visit. Patient eDiaries will be reviewed by the study center personnel on Day 1 to ensure that they are being completed correctly. The data collected for 7 consecutive days (Day -7 to Day -1) prior to the Day 1 visit will be used as baseline data for weekly score. The patient eDiary questions for efficacy assessments will consist of urticaria activity score (UAS; itch severity score [ISS] and hives severity score [HSS]), angioedema episodes, and rescue medication use. Patients should be encouraged to make every effort to stay abreast with their patient eDiary entries, even when traveling or in a location where data reception connectivity will not allow daily transfer of eDiary entries to the central server. When data reception connectivity is not available, data entries will be stored locally in the eDiary application and transferred at the time that such connectivity becomes available.

6.1.1.1 Itch Severity Score

The ISS will be recorded twice daily (morning and evening) in the patient eDiary, on scale of 0 (none) to 3 (severe) points (Table 6-1). The daily ISS is the average of the morning and evening scores and the ISS7 is the sum of the daily ISS over 7 days.

The MID is the smallest difference in scores considered clinically meaningful. The MID for ISS7 is defined as a reduction of 5 points or more from baseline (Mathias *et al.,* 2012).

6.1.1.2 Hives Severity Score

The HSS, defined by number of hives, will be counted twice daily (morning and evening) in the patient eDiary, on a scale of 0 (none) to 3 (intense) points (Table 6-1). The daily HSS is the average of the morning and evening scores, and the HSS7 is the sum of the daily HSS over 7 days.

6.1.1.3 Urticaria Activity Score

The UAS will be calculated as the sum of the ISS and the HSS by diary-based documentation (Table 6-1). The sum of the scores represents disease severity on a scale from 0 (minimum) to 6

(maximum). The daily UAS is the average of the morning and evening scores and the UAS7 is the sum of the daily UAS over 7 days.

Table 6-1 Urticaria Activity Score Scale

Score	Itch Severity	Hive Severity
0	None	None
1	Mild (present but not annoying or troublesome)	Mild (1-6 hives/12 hour)
2	Moderate (troublesome but does not interfere with normal daily activity or sleep)	Moderate (7-12 hives/12 hour)
3	Severe (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)	Intense (> 12 hives/12 hour)

6.1.1.4 Angioedema Episodes

The patient will have to record information regarding angioedema episodes daily in the patient eDiary. This will be checked whether there is rapid swelling on face, inside mouth, or elsewhere on the body and the actions and/or treatments taken related to those angioedema occurrences.

6.1.1.5 Rescue Medication Use

The patient will record the number of tablets of rescue medication used over the past 24 hours to control conditions such as itch or hives once daily in the eDiary.

6.1.2 Handling of Missing Data

6.1.2.1 Calculation of Weekly Scores

The weekly score is the sum of the average daily scores over 7 days each week. The daily scores are calculated as the average of the morning and evening scores based on daily patient eDiary entries. When either the morning or evening score is missing, the non-missing score for that day (morning or evening) will be used as the daily score.

When one or more of the daily scores are missing, the following principles will be applied;

- If a patient has at least 4 non-missing daily scores included in the calculation of the weekly score (as defined in Section 7.4.2.1), the weekly score is calculated as the sum of the available patient eDiary scores in that week, divided by the number of days that have a non-missing diary score, multiplied by 7.

- If there are less than 4 non-missing daily scores included in the calculation of the weekly score (as defined in Section 7.4.2.1), then the weekly score is missing for the week.

The examples of calculating weekly scores is shown in Table 6-2.

All weekly scores will include UAS7, ISS7, and HSS7.

Table 6-2 Example of Weekly Score Calculation

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Morning	3	3	missing	missing	2	2	1
Evening	3	missing	missing	missing	3	1	1
Daily score	3	3	missing	missing	2.5	1.5	1
Weekly score calculation: [(3 + 3 + 2.5 + 1.5 + 1) / 5] × 7 = 15.4							

6.1.2.2 Missing data imputation

Missing data of ISS7 at Week 12 will be imputed using the approach of multiple imputation for the primary efficacy analysis. Multiple imputation with the missing at random assumption will be applied using MI procedure in Statistical Analysis System Software (SAS). All patients with Baseline ISS7 score in mITT Set will be included in the analysis. The multiple imputed datasets will be generated based on linear regression models on ISS7 at Week 12 with treatment group as a fixed effect and baseline ISS7, body weight on Day 1, and country (or region) as covariates. The 10 imputed datasets will be generated. These multiple imputed datasets are then analyzed by using the analysis method specified in Section 7.4.2.2.1. The results from each set of imputed datasets will then be pooled using MIANALYZE procedure in SAS.

6.2 Quality of Life Assessments

The patient will record the validated DLQI and CU-Q_2oL in the eDiary at the scheduled time point specified in the schedule of assessments (Appendix 1).

6.2.1 Dermatology Life Quality Index

The DLQI is a 10-item dermatology-specific health-related questionnaire across 6 domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment (Finlay *et al.,* 1994). Patients will rate their dermatology symptoms as well as the impact of their skin condition on various aspect of their lives. Each question is scored from 0 to 3. Overall score, on scale of 0 to 30, will be calculated by summing the individual domain scores. The DLQI will be measured at the time point specified in the schedule of assessments (Appendix 1).

6.2.2 Chronic Urticaria Quality of Life Questionnaire

The CU-Q_2oL is a 23-item CSU-specific based health-related QoL questionnaire across 6 domains: pruritus, swelling, impact on life activities, sleep problems, limits, and looks. Patients will rate their CSU symptoms and the impact of their CSU on various aspects of their lives. Each question is scored from 1 (not at all) to 5 (extremely), and overall raw score, on a scale of 23 to 115, is calculated by summing the individual raw domain scores (Baiardini I *et al.*, 2005). The CU-Q_2oL will be measured at the time point specified in the schedule of assessments (Appendix 1).

6.3 Pharmacokinetic Assessments

Pharmacokinetic blood samples for the determination of serum concentration of study drug will be collected at the time points specified in the schedule of assessments (Appendix 1). If a patient discontinues the study drug during treatment periods, the blood sample for PK assessments should be collected only at the right next scheduled visit of the last study drug administration visit and EOS visit (e.g., if a subject discontinues the study drug after Week 4 administration, blood sample for PK assessment will be collected at Week 8 and EOS visit).

If the blood sample is unable to be analyzed or is missing at certain time point, some blood samples collected for immunogenicity assessment at same time point can be used for PK assessment. Analysis will be performed at the central laboratory.

Actual sampling times for each patient will be recorded in the patient's eCRF and individual source documents. Instructions for the blood collection, storage, and shipment to the central laboratory is described in Sections 6.5 and 6.6.2.

Details of the PK endpoint and PK analysis will be provided in the statistical analysis plan (SAP).

6.4 Safety Assessments

Safety assessments will consist of monitoring and recording protocol-defined AEs, SAEs, AESIs (allergic reaction type I/anaphylaxis, injection site reactions, allergic reaction type III [serum sickness/serum sickness-like reaction] and parasitic [helminth] infections), immunogenicity including antidrug antibody and neutralizing antibody, total and free serum IgE, viral serology testing, C3, C4, and total hemolytic complement (CH_{50}) assessments, hypersensitivity monitoring (via vital sign and ECG when indicated), physical examination, measurement of hematology, clinical chemistry, and urinalysis variables, measurement of vital signs, ECG, and body weight, pregnancy testing, and prior and concomitant medications.

Retest of any assessments during the Screening Period in terms of safety may be done at the Investigator's discretion if medically justifiable.

6.4.1 Medical History, Disease History, and Demographic Information

The medical history (general medical history and medication history), disease history of CSU, and demographic information (age, sex, ethnicity, race, and body mass index [kg/m²]) will be recorded on both the source documents and eCRF.

6.4.2 Adverse Events

6.4.2.1 Definitions of Adverse Events

An AE is defined as any untoward medical occurrence in any patient during the study which does not necessarily have a causal relationship with the study drug. Any new condition noted at Screening would be regarded as an AE, but not a treatment-emergent AE (TEAE).

Adverse events requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Treatment due to an AE will be recorded.

A TEAE includes any untoward medical occurrence in a patient after administration of an investigational study treatment, which does not necessarily have to have a causal relationship with this treatment. A TEAE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the product, whether or not related to the investigational study treatment.

Abnormal results of diagnostic procedures including laboratory test abnormalities are considered as AEs if they fulfill the following criteria:

- Result in discontinuation from the study treatment
- Require treatment or any other therapeutic intervention
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)
- Are clinically significant as evaluated by the Investigator

Disease progression of CSU will not be recorded as an AE or SAE. Medical intervention such as surgery, diagnostic procedures, and therapeutic procedures are not AEs, but the action taken to treat the medical condition. They should be recorded as treatment(s) of the AEs. The event term

of primary cause should be recorded and reported instead of the term of surgery, diagnostic procedure, or therapeutic procedure.

6.4.2.1.1 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (refers to an AE in which the patient was at immediate risk of death at the time of event). It does not refer to an event which may have caused death, if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in the definition above. These should also be considered serious. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Adverse events associated with hospitalization or prolongations of hospitalization are considered as SAEs. Any admission (even if < 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, from medical floor to a coronary care unit, from neurological floor to a tuberculosis unit).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include the following:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or worsening of the pre-existing condition (for work-up of persistent pre-treatment laboratory abnormality)
- Social admission (e.g., patient has no place to sleep)
- Purely for convenience (e.g., for easier performance of study assessments)

- Administrative admission (e.g., for yearly physical examination)
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Pre-planned treatments or surgical procedures; these should be noted in the baseline documentation for the entire protocol and/or for the individual patient
- Hospitalization solely due to disease progression without any other AEs as decided by the Investigator

6.4.2.1.2 Unlisted (Unexpected) Serious Adverse Events

An unlisted or unexpected SAE is defined as an event of which the nature or severity is not consistent with the applicable reference documents (e.g., study drug IB).

6.4.2.1.3 Suspected Unexpected Serious Adverse Reactions

The Sponsor will promptly evaluate all SUSARs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single SAE cases, the Sponsor will assess the expectedness of these events using the applicable reference documents (e.g., IB).

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6.4.2.1.4 Adverse Events of Special Interest

The following AEs are considered as AESIs and will be closely monitored by Investigator and reported using the same process as for AEs.

Allergic reaction type I/anaphylaxis

All AEs related to type I local or systemic allergic reactions including anaphylaxis and anaphylactic shock will be included. Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. Diagnosis of anaphylaxis will be based on the anaphylaxis criteria of

National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (Sampson *et al.,* 2006).

Injection site reactions

All AEs related to injection site reaction could include but are not limited to the following: erythema, pain, pruritus, haematoma, hemorrhage, swelling, urticaria, induration, bruising, irritation, paresthesia, rash, tenderness with or without symptoms (e.g., warmth, erythema, or itching), lipodystrophy, edema, ulceration, necrosis, severe tissue damage.

Allergic reaction type III (serum sickness/serum sickness-like reactions)

All AEs related to allergic reaction type III include but are not limited to the following: arthritis/arthralgias, rash, fever and lymphadenopathy with an onset 1 to 5 days after the administration. Although circulating immune complexes or a skin biopsy consistent with a type III reactions are not seen with this event, the signs and symptoms are similar to those seen in patients with serum sickness.

Parasitic (helminth) infections

All AEs related to parasitic (helminth) infection include but are not limited to the following: cestode infections, nematode infections and trematode infections.

6.4.2.1.5 Eliciting and Documenting Adverse Events

All AEs will be reported by the Investigator via eCRF from the date patients signs the ICF until EOS visit, regardless of the relationship to the study drug. The condition of the patient will be monitored throughout the study for any signs or symptoms. After the EOS visit, serious adverse drug reactions will be reported to the Sponsor or its designee.

At every study visit, patient will be asked a standard non-leading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to patient observations, AEs identified from any study data (e.g., laboratory values, physical examination findings, ECG changes) or identified from review of other documents that are relevant to patient safety will be documented on the AE page in the eCRF.

6.4.2.1.6 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF and source documents. Information to be collected includes drug treatment, action taken with study treatment, event term, date/time of onset and end date, Investigator-specified assessment of severity and relationship to study treatment, seriousness of AE, any required treatment or evaluations, and outcome.

Adverse events resulting from concurrent illness, reactions to concurrent illnesses, or reactions to concurrent medications must also be reported from the date patients signs the ICF until EOS visit. Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE Version 5.0). The Medical Dictionary for Regulatory Activities will be used to code all AEs.

Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

The Investigator's assessment of an AE's relationship to study treatment is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported.

The severity and the relationship or association of the study treatment in causing or contributing to the AE will be characterized as defined in Sections 6.4.2.2 and 6.4.2.3, respectively.

6.4.2.1.7 Reporting Serious Adverse Events

Any AE considered serious by the Investigator or which meets SAE criteria (Section 6.4.2.1.1) must be reported to [redacted] PVG within 24 hours from the time study center staff first learn about the event. Data entry should be completed in the remote data capture system by the Investigator within 24 hours of awareness of an SAE. In the event that this is not possible (e.g., system failure or access problems), the study center should complete an SAE report form and email it to [redacted] PVG [redacted] or via FAX (details on SAE report form) within 24 hours of awareness of the event. The remote data capture system should be updated as soon as it is available. Withdrawal from the study and all therapeutic measures will be at the discretion of the Principal Investigator or Sub-Investigator. All SAEs will be followed up as specified in Section 6.4.2.1.8.

The Sponsor or its designee is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating Investigators, in accordance with

European Clinical Trials Regulation (Regulation [EU] No 536/2014), International Council for Harmonisation (ICH) guidelines, and/or local regulatory requirements.

The Sponsor or its designee is responsible for reporting fatal or life-threatening SUSARs (expedited reports) to the regulatory agencies and competent authorities within 7 calendar days after being notified of the event. The Sponsor or its designee should report other relevant SAEs associated with the use of the study drug to the appropriate competent authorities (according to local guidelines), Investigators, and IECs by a written safety report within 15 calendar days of notification.

6.4.2.1.8 Follow-up of Adverse Events

All reported AEs will be followed until one of the following: resolution or improvement from baseline, confirmed by the Investigator that no further improvement could be expected, no more collection of clinical or safety data, or final database closure. For patients who withdraw from the study, the last assessed status of AEs will be collected.

6.4.2.2 Assessment of Severity

The severity of an AE refers to the extent to which an AE affects the patient's daily activities.

The severity of the AE will be graded based on the CTCAE Version 5.0, based on the following general guidelines (a semicolon indicates "or" within each description):

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)[1]

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2]

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

1. Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

2. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

If an AE upgrades in severity or changes from nonserious to serious, a new AE needs to be reported. If an AE downgrades in severity, it should not be reported as a new AE.

6.4.2.3 Assessment of Causality

As discussed in Section 6.4.2.1.6, the Investigator's assessment of an AE's relationship to study treatment is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported.

The relationship or association of CT-P39 or Xolair in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study treatment and the reported event.

Possible: This relationship suggests that treatment with the study treatment caused or contributed to the AE, e.g., the events follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study treatment but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the Investigator's clinical experience, the association of the event with the study treatment seems likely. The event disappears or decreases on cessation or reduction of the dose of study treatment.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease states, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study treatment is re-administered.

6.4.3 Other Safety Assessments

6.4.3.1 Immunogenicity Assessment

The immunogenicity of CT-P39 and Xolair will be assessed by antidrug antibody and neutralizing antibody test in validated immunoassay. Blood samples for immunogenicity assessments will be collected at the time points specified in the schedule of assessments (Appendix 1). If the blood sample is unable to be analyzed or is missing at certain time point, some blood samples collected for PK assessment at the same time point can be used for immunogenicity assessment. Additional immunogenicity will be assessed when immune-related AEs occurs. Immune-related AEs are defined as the following but are not limited:

- Allergic reaction type I
- Allergic reaction type III

Blood samples for immunogenicity for patients with immune-related AEs will be obtained on onset date of immune-related AEs, if possible, or blood sample can be used if it is obtained at the same date of study drug administration.

Analysis will be performed at the central laboratory.

Instructions for the blood collection, storage, and shipment is described in Sections 6.5 and 6.6.2.

6.4.3.2 Injection Site Reaction

Injection site reactions will be assessed 30 minutes (± 10 minutes) after the end of the study drug administration, as specified in the schedule of assessments (Appendix 1).

Details will be recorded in both the eCRF and source documents.

6.4.3.3 Hypersensitivity/Allergic Reaction Monitoring

Hypersensitivity/allergic reactions will be assessed before study drug administration (within 30 minutes) and 1 hour (± 10 minutes) after the end of the study drug administration, as specified in the schedule of assessments (Appendix 1). Hypersensitivity/allergic reactions will be assessed by additional vital sign measurements including blood pressure, heart and respiratory rates, and body temperature. Patients will remain in study center for anaphylaxis observation for 2 hours after study drug administration in the Treatment Period I and an hour after the study drug administration in the Treatment Period II. If patients have signs and symptoms of hypersensitivity/allergic reactions at home (hives, difficulty breathing, or swelling of face, eyes, lips, or mouth or any symptoms of cardiac origin), patients or caregivers should be advised to call the study center or get immediate help.

In addition, hypersensitivity will be monitored by routine continuous clinical monitoring. In case of hypersensitivity, emergency medication and equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available and any types of ECG can be performed at the Investigator's discretion.

For patients who experience or develop life-threatening treatment-related hypersensitivity/allergic reactions, study drug must be stopped immediately, and the patient will be discontinued from the study drug.

In case of allergic reaction type I, additional immunogenicity sampling will be performed to monitor immune-related AE.

In case of allergic reaction type III, including serum sickness/serum sickness-like reactions (arthritis/arthralgias, rash, fever, lymphadenopathy), the patient will be asked to visit the study center at the earliest time point that patient recognize allergic reaction type III. The following assessments will be additionally performed to determine serum sickness/serum sickness-like reactions during the study:

- Immunogenicity
- Clinical laboratory analyses
- Complement (C3 and C4) and total hemolytic complement (CH_{50})

Details will be recorded in both the source documents and the eCRF.

6.4.3.4 Vital Signs, Weight, and Height

Vital signs and weight measurements will be performed at the time points specified in the schedule of assessments (Appendix 1). Vital signs (including blood pressure, heart and respiratory rates, and body temperature) will be assessed before the study drug administration and be measured after 5 minutes of rest. Height will be assessed at Screening only as a baseline measurement. Details will be recorded in both the eCRFs and source documents.

Vital sign measurements will also be monitored before and after the study drug administration as part of the hypersensitivity monitoring (Section 6.4.3.3).

6.4.3.5 Electrocardiogram

All scheduled 12-lead ECGs will be performed after the patient has rested quietly for at least 5 minutes. A 12-lead ECG will be performed at the time points specified in the schedule of assessments (Appendix 1) and if the patient experienced cardiac symptoms during study drug administration. If following the ECG review by the Investigator there are any ECG findings that would indicate cardiac insufficiency or QT prolongation (e.g., QTc Frederica prolongation > 450 milliseconds, or any other abnormalities), the patient will be referred to a cardiologist to confirm the abnormality. The Investigator will then report the event in the eCRF and source documents. Regardless of 12-lead ECG result, further evaluation with a cardiologist can be done depending on the Investigator's discretion.

In case of hypersensitivity monitoring, any type of ECG can be performed at the Investigator's discretion (Section 6.4.3.3).

6.4.3.6 Physical Examination

Investigators should carefully evaluate patients for any indication of injection site reactions, allergic reaction type I/anaphylaxis, allergic reaction type III (serum sickness/serum sickness-like reactions) and parasitic (helminth) infections and treatment indicated in accordance with the Investigator's medical judgment. Physical examination will be performed at the time points specified in the schedule of assessments (Appendix 1).

Information about the physical examination will be recorded by the Investigator or designee (e.g., physician) in the eCRF and source documents. Any abnormalities will be recorded in the source documents and eCRF. Clinically significant findings and illnesses reported after the start of the study that meet the definition of an AE will be recorded in the eCRF and source documents.

6.4.3.7 Viral Serology

During the Screening Period, viral serology tests will be performed for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), hepatitis C antibody, and HIV-1 and -2 in all patients (mandatory).

If the HBsAg test result is positive, the patient will be excluded. If a patient is HBsAg negative and HBcAb is positive, regardless of HBsAb results, a hepatitis B virus (HBV) DNA test will be performed at Screening. In this case the patient is eligible for this study only when the HBV DNA test result is negative (Table 6-3). For patient who were enrolled based on the HBV DNA test, testing of HBsAg, HBsAb, and HBV DNA will be performed at EOT (Week 24) and EOS visits for monitoring purposes. During the study, if hepatic symptoms are suspected, tests should be performed. If the patient develops hepatitis B reactivations, the study drug must be stopped.

Table 6-3 Eligibility Based on Serologic Markers for Hepatitis B Infection

Test Results				Eligibility
HBsAg	HBsAb	HBcAb	HBV DNA	
+	+/–	+/–	Not applicable	Not eligible
–	+/–	+	+	Not eligible
–	+/–	+	–	Eligible
–	+/–	–	Not applicable	Eligible

Abbreviations: DNA = deoxyribonucleic acid; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.

If hepatitis C antibody result is positive, the patient will be excluded from the study except for the case that the patient was adequately treated and completely recovered from the past hepatitis C infection.

If the HIV test result is positive, the patient will be excluded from the study.

Analysis will be performed at the central laboratory.

6.4.3.8 Stool Ova and Parasite Evaluation

The stool ova and parasite evaluation should be performed at Screening in patients who have at least one of the risk factors listed below and an absolute eosinophil count of > 2 times the ULN at Screening.

- Travel within 6 months before the first study drug administration to or living in an endemic area of parasitic infection
- Chronic gastrointestinal symptoms
- Chronic immunosuppression

Analysis will be performed at the central laboratory.

6.4.3.9 Pregnancy

Patient and their partner of childbearing potential must agree to use contraception methods as specified in Section 4.1.1 throughout the study period. Although a patient withdraw from the study after the study drug administration, the patient and their partner of childbearing potential must use the specified contraception methods for 3 months after the last dose of study drug.

For women of childbearing potential, a serum pregnancy test will be conducted at Screening and EOS visit. Only patients with a negative serum pregnancy test results can be enrolled in the study.

Urine pregnancy test will be performed prior to dosing during all Treatment Period visits and EOT (Week 24) visit and any time if pregnancy is suspected (Appendix 1). If a urine pregnancy test result is found equivocal or positive, a confirmatory serum pregnancy test will be performed.

Urine Pregnancy test samples will be analyzed at the local laboratory and serum pregnancy test samples will be analyzed at the central laboratory.

In an event of unexpected pregnancy during the study participation, patients will be counseled to inform the Investigator. If a female patient or female partner of a male patient becomes pregnant, the pregnancy must be reported to the Sponsor and [redacted] within 24 hours of the study center's knowledge of the likelihood of pregnancy while confirmation is pending. Once the pregnancy is confirmed with a serum pregnancy test, female patients must permanently discontinue the study drug. The study center must complete the supplied pregnancy form (female patient or partner of a male patient) and return it to the Sponsor and [redacted] within 24 hours of pregnancy being detected.

Pregnant patients or the pregnant partners of male patients will be followed until the end of the pregnancy (e.g., delivery, stillbirth, miscarriage) and the mother and the baby will be followed for 1 year after the birth, provided consent is obtained.

In female patients, abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs. Any SAE that occurs during pregnancy (e.g., maternal serious complications, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) must be reported within 24 hours in accordance with the procedure for reporting SAEs (Section 6.4.2.1.7).

6.4.3.10 Clinical Laboratory Analyses

Blood and urine samples for clinical laboratory assessments will be collected at the time points specified in the schedule of event (Appendix 1). Blood samples do not need to be performed in a fasting state unless required in the opinion of the Investigator.

The following clinical laboratory analyses will be performed.

Clinical chemistry: Total protein, sodium, potassium, calcium, chloride, magnesium, inorganic phosphate, albumin, glucose, total cholesterol, triglycerides, C-reactive protein, urea, creatinine, uric acid, bilirubin (total, direct), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, lactate dehydrogenase, creatine phosphokinase, and creatine kinase-myocardial band isoenzyme

Hematology: Hemoglobin, hematocrit, red blood cell count, total and differential white blood cell, absolute lymphocyte count, absolute neutrophil count, absolute eosinophil count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, and platelet count

Urinalysis: Color, pH, specific gravity, glucose, ketones, nitrite, protein, bilirubin, urobilinogen, blood, leucocyte, and microscopic examination

Clinical laboratory test samples will be analyzed at the central laboratory.

6.4.3.11 C3, C4, and Total Hemolytic Complement (CH_{50}) Assessments

Complement (C3 and C4) and total hemolytic complement will be assessed on Day 1 prior to the study drug administration (Appendix 1) to establish the baseline value. Additional clinical laboratory test samples will be collected and C3, C4, and total hemolytic complement (CH_{50}) will be assessed in the case of allergic reaction type III, including serum sickness/serum sickness-like reactions (e.g., arthritis/arthralgias, rash, fever, lymphadenopathy).

C3, C4, and total hemolytic complement (CH_{50}) test samples will be analyzed at the central laboratory.

6.4.3.12 Total and Free IgE Assessments

Blood samples for total and free IgE assessments will be collected at the time points specified in the schedule of assessments (Appendix 1).

Total and free IgE samples will be analyzed at the central laboratory.

6.5 Sample Collections

The total volume of blood collected for each assessment is discussed in each specific laboratory manual. The sample collection tube may be changed during the study and details will be provided in the laboratory manual.

6.5.1 Pharmacokinetic Blood Sampling

Blood samples for PK assessments will be obtained in accordance with the laboratory manual from each patient at the time point specified in the schedule of assessments (Appendix 1). All samples should be collected as close as possible to the scheduled time point. The actual sampling date and time will be recorded in both the eCRF and source documents.

6.5.2 Immunogenicity Blood Sampling

Blood samples for immunogenicity assessments will be obtained in accordance with the laboratory manual from each patient at the time point specified in the schedule of assessments (Appendix 1) or when immune-related AEs occur. All samples should be collected as close as possible to the scheduled time point. The actual sampling date and time will be recorded in both the eCRF and source documents.

6.5.3 Stool Ova and Parasite Evaluation

A stool sample will be collected during Screening for ova and parasite examination on patients with an absolute eosinophil count > 2 times the ULN at Screening AND risk factors for parasitic disease listed in exclusion criterion #5 (Section 4.1.2). The actual sampling date will be recorded in both the eCRF and source documents.

6.5.4 Urine Sampling

Urine samples for safety (clinical laboratory testing) and urine pregnancy test will be collected for analysis at the time points specified in the schedule of assessments (Appendix 1). The actual sampling date will be recorded in both the eCRF and source documents.

6.5.5 Safety Blood Sampling

Blood samples for safety (clinical laboratory testing, total and free IgE testing, and C3, C4, and total hemolytic complement [CH_{50}]) and serum pregnancy test will be collected for analysis throughout the study at the time points specified in the schedule of assessments (Appendix 1). The

actual sampling date will be recorded in both the eCRF and source documents. Actual sampling time will also be recorded in both the eCRF and source documents for total and free IgE samples.

6.6 Labeling, Storage, and Transportation of Samples

6.6.1 Sample Labeling

Each sample tube will be clearly labeled with the following information: study number, patient number, tube identification and scheduled sampling time point.

6.6.2 Sample Storage and Shipment

During the study, blood samples will be collected for PK, immunogenicity, and safety analyses.

Where appropriate, the serum should be transferred into a sufficient number of transfer tubes for transport to assigned testing facilities. Primary and back-up samples will be shipped to the central laboratory according to the laboratory manual, and primary samples should be shipped separately from the back-up samples.

Additionally, back-up samples for PK, immunogenicity, and free IgE will be retained at the central laboratory as a back-up for up to 5 years after the end of the study in case additional analysis is required. Blood samples collected for free IgE assessment can be used for additional analysis for either free or total IgE. If additional analysis for PK, immunogenicity, and IgE is not required, the sample will be stored at the Sponsor or a designated biobank for a further 5 years (from the date the sample is transferred to the Sponsor/biobank) unless a specific authorization is given by the Sponsor to destroy the sample. Additional tests can be conducted at the Sponsor or the biobank if it is required from a regulatory or medical perspective. Details in storage and shipment will be followed according to the laboratory manual.

7 Statistical Analysis

The statistical analysis will be performed using SAS Version 9.4 or higher (SAS institute Inc., Cary, North Carolina, US). The statistical methods for this study will be described in a detailed SAP, which will be finalized before database lock. Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the CSR.

Full details of the statistical methods will be described in the SAP.

7.1 Sample Size Calculation

Sample size was derived based on a power analysis using PASS (Version 16.0, NCSS Statistical Software, LLC. Utah, US). A total of 600 patients will be randomized in a 2:2:1:1 ratio to 300 mg of CT-P39 (Arm 1), 300 mg of Xolair (Arm 2), 150 mg of CT-P39 (Arm 3), and 150 mg of Xolair (Arm 4) treatment arms, respectively.

For the demonstration of the therapeutic similarity between 300 mg of CT-P39 (Arm 1) and 300 mg of Xolair (Arm 2) in the mean change from baseline in ISS7 at Week 12, a sample size of 400 patients (200 patients per each arm) achieves approximately 95% statistical power based on the two one-sided 5% significance level and an equivalence margin of [− 2.5, + 2.0]. In the sample size calculation, the common SD of the mean change from baseline in ISS7 at Week 12 is assumed to be 5.95 and the expected mean difference to be 0.

In order to support assay sensitivity and to evaluate the relative potency between CT-P39 and Xolair, additional 200 patients will be enrolled in 150 mg doses arms (100 patients in each of CT-P39 [Arm 3] and the Xolair [Arm 4] treatment arms). Using the observed mean and SD of change from baseline in ISS7 at Week 12 from ASTERIA I Study (Saini *et al.,* 2015), which has the most similar study design to this study, a total sample size of 600 patients (200 patients for 150 mg dose arms and 400 patients for 300 mg or dose arms) achieves an approximately 97% statistical power to demonstrate similarity using the relative potency of CT-P39 to the Xolair using a predefined margin of [0.5, 2.0].

7.2 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Randomized Set: The randomized set is defined as all randomly assigned patients prior to dosing on Day 1 regardless of whether they received any study drug (CT-P39 or Xolair).

Modified intent-to-treat (mITT) Set: The mITT Set is defined as all randomly assigned patients who receive at least one full dose of either of the study drugs during the Treatment Period I. Patients will be analyzed to the arm they are randomized.

Per-Protocol (PP) Set: The PP Set is defined as all randomly assigned patients who receive all 3 doses of study drug during the Treatment Period I and have an ISS7 assessment at Week 12. Patients with major protocol deviation that may affect the interpretation of study results of primary efficacy endpoint will be excluded from the PP Set. Final determination of the PP Set will be made on case-by-case manner at the blinded data review meeting.

Pharmacokinetic Set: The PK Set is defined as all patients who receive at least one full dose of either of the study drugs during the Treatment Period I and have at least one post-treatment PK result prior to dosing at Week 12. If any patients are found to be noncompliant with respect to dosing, a determination of the PK Set will be made on a case-by-case basis at the blinded data review meeting.

Safety Set: The Safety Set is defined as all randomly assigned patients who receive at least one dose (full or partial) of study drug. Patients will be analyzed to the arm they are actually treated.

7.3 Description of Subgroups to be Analyzed

Subgroup analysis could be implemented to reflect medical, regulatory, regional, or ethnic consideration, if required.

7.4 Statistical Analysis Methodology

7.4.1 General Consideration

Continuous variables will be summarized by reporting the following descriptive statistics: the number of observations (n), mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency tables showing the number and percentage of patients within a particular category. Data will be listed in data listings.

7.4.2 Analysis of Efficacy Endpoints

7.4.2.1 Determination of Study Week for Weekly Scores

The study weeks for calculation of weekly score endpoints are defined in Table 7-1. The baseline weekly score is comprised of 7 days prior to Day 1 (Day -7 to -1). Time period over which the data are used in the calculation of each weekly score will be determined based on this.

Table 7-1 Protocol-defined Study Week Definitions

Week	Day	Week	Day	Week	Day	Week	Day
1	1 – 7	**11**	71 – 77	**21**	141 – 147	**31**	211 – 217
2	8 – 14	**12***	78 – 84	**22**	148 – 154	**32**	218 – 224
3	15 – 21	**13**	85 – 91	**23**	155 – 161	**33**	225 – 231
4*	22 – 28	**14**	92 – 98	**24**	162 – 168	**34**	232 – 238
5	29 – 35	**15**	99 – 105	**25**	169 – 175	**35**	239 – 245
6	36 – 42	**16***	106 – 112	**26**	176 – 182	**36**	246 – 252
7	43 – 49	**17**	113 – 119	**27**	183 – 189	**37**	253 – 259
8*	50 – 56	**18**	120 – 126	**28**	190 – 196	**38**	260 – 266
9	57 – 63	**19**	127 – 133	**29**	197 – 203	**39**	267 – 273
10	64 – 70	**20***	134 – 140	**30**	204 – 210	**40**	274 – 280

* Indicates week prior to a study treatment visits except for Week 1. For example, the Week 4 study visit occurs on Day 29, and Week 4 weekly scores are based on Day 22 to 28.

In situations where a study treatment visit occurs before or after the protocol-specified visit day, the following principles will be applied to determine from which study days the data will be used to compute the weekly scores. If a patient visits the site later than the planned visit date, the collected daily score from the planned visit date to the day before the actual visit date will not be considered for the weekly score.

- **Weeks prior to a study treatment visit (Week 4, 8, 12, 16, and 20):** The time period of the study week starts from the first study day of that week (Table 7-1) and ends at the earlier of the last study day of the week or the day before the study treatment visit.
- **Weeks following a study treatment visit (Week 1, 5, 9, 13, 17, and 21)**: The time period of the study week starts from the latter of the first study day of the week or the study day on which the treatment visit occurred and ends on the last study day of the week (Table 7-1).

The examples of patient visits and the study days used to calculate the weekly scores are shown in Table 7-2.

Table 7-2 Examples of Study Week Determination

	Protocol-defined	Example 1	Example 2	Example 3
Week 4 visit	Day 29	Day 27	Day 32	Day 33
Time period for Week 4	Day 22 – 28	Day 22 – 26	Day 22 – 28	Day 22 – 28
Time period for Week 5	Day 29 – 35	Day 29 – 35	Day 32 – 35	Day 33 – 35

Note: In case of example 3, weekly scores for Week 5 will be missing since only 3 non-missing daily scores can be collected according to Section 6.1.2.1.

7.4.2.2 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in ISS7 at Week 12. Analyses will be assessed using two approaches. The first co-primary efficacy evaluation is to compare mean change from baseline in ISS7 of 300 mg arms at Week 12. If a patient has missing data of ISS7 at Week 12, missing data will be imputed as described in Section 6.1.2.2.

The other co-primary efficacy evaluation is to assess relative potency of CT-P39 compared to Xolair. The primary efficacy analyses will be conducted on the mITT Set and a supportive analysis will be repeated using the PP Set. To assess the robustness, a tipping point approach will be applied, where by the impact of missing data on the conclusions from the primary analysis of mean change from baseline will be assessed.

7.4.2.2.1 Comparison of the Mean Change from Baseline in ISS7 of 300 mg Arms at Week 12

One of the primary efficacy evaluations is to compare mean change from baseline in ISS7 of 300 mg of CT-P39 and 300 mg of Xolair at Week 12.

Comparison of the mean change from baseline in ISS7 of CT-P39 300 mg treatment arm and Xolair 300 mg treatment arm at Week 12 will be analyzed using an analysis of covariance model with treatment as a fixed effect and baseline ISS7, body weight and country as covariates. Final determination of covariates and details will be described in the SAP. The difference of least squares means between 300 mg of CT-P39 (Arm 1) and 300 mg of Xolair (Arm 2) will be calculated based on aforesaid analysis of covariance model. Statistical equivalence will be declared if the two-sided 90% confidence interval (CI) of the difference falls entirely within an equivalence margin, [− 2.5, + 2.0].

7.4.2.2.2 Relative Potency

The other primary efficacy evaluation is the relative potency of CT-P39 compared with Xolair in terms of change from baseline in ISS7 at Week 12.

The relative potency of CT-P39 to the Xolair is defined as the dose of CT-P39 that produces the same biological response as one unit of the dose of the Xolair. The biological response will be estimated by the change from baseline in ISS7 at Week 12. Since the 2 treatments will be compared at the same 2-dose levels (300 mg and 150 mg), a 4-point assay will be used to calculate the relative potency and its CI. Statistical equivalence in terms of the relative potency will be declared if the two-sided 90% CI of the relative potency falls entirely within an equivalence margin [0.5, 2.0].

7.4.2.3 Analysis of Secondary Efficacy Endpoints

All secondary efficacy endpoints will be analyzed using the mITT and PP Sets. These will be summarized by treatment arm as appropriate and listed. In case of calculating parameters defining "responder and non-responder", the patient will be classified as a non-responder if a patient has missing weekly scores for the given week.

7.4.2.3.1 Weekly Itch Severity Score

The change from baseline in ISS7 at Week 8 will be calculated as ISS7 at Week 8 minus the baseline ISS7. The change from baseline in ISS7 at Week 24 will be calculated similarly.

Descriptive statistics for actual value and change from baseline will be summarized by each treatment group.

7.4.2.3.2 Time to MID Response in ISS7

The MID for ISS7 is defined as a reduction of 5 points or more from baseline. Time to MID response in ISS7 is the time (in week) from Day 1 to the study week when MID response for ISS7 is first achieved; that is, the study week for which the change from baseline in ISS7 is ≤ -5.

Time to MID response in ISS7 will be estimated by Week 12. If a patient fails to achieve a MID response up to Week 12, it will be calculated censoring at the date of the last non-missing ISS7 evaluation up to Week 12. If a patient discontinues treatment prior to Week 12 without achieving a MID response, this endpoint will be censored as of the day of treatment discontinuation.

The median and its corresponding 95% CI, minimum and maximum of time to first MID response in ISS7 for each treatment group will be estimated using the Kaplan-Meier method. Kaplan-Meier estimates of the distribution of time to first MID response in ISS7 will be presented graphically.

7.4.2.3.3 Percentage of MID Responder in ISS7

The proportion of patients achieving MID response in ISS7 at Weeks 8, 12, and 24 will be summarized by each treatment group.

7.4.2.3.4 Change From Baseline in UAS7

Descriptive statistics for actual value and change from baseline in UAS7 at Weeks 8, 12, and 24 will be summarized by each treatment group.

7.4.2.3.5 Percentage of Patients with a UAS7 ≤ 6 Points

The number and percentage of patients who achieve UAS7 of 6 points or less (UAS7 ≤ 6 points) at Weeks 8, 12, and 24 will be summarized by each treatment group.

7.4.2.3.6 Percentage of Complete Responder in UAS7

The number and percentage of patients who achieve complete response in UAS7 (UAS7 = 0 points) at Weeks 8, 12, and 24 will be summarized by each treatment group.

7.4.2.3.7 Change From Baseline in the HSS7

Descriptive statistics for actual value and change from baseline in HSS7 at Weeks 8, 12, and 24 will be summarized by each treatment group.

7.4.2.3.8 Percentage of Angioedema-Free Days

The percentage of angioedema-free day will be defined as the number of days for which the patient indicated a ‘No’ response to the angioedema question in the patient eDiary divided by the total number of days with a non-missing diary entry starting on the Week 4 visit date and ending the day prior to the Week 12 visit date. Patients who withdraw before the Week 4 visit or who have missing responses for > 40% of the daily diary entries between the Week 4 study visit and the Week 12 study visit will not be included in this analysis. No imputations will be made for missing data. Descriptive statistics of the percentage of angioedema-free days from Weeks 4 to 12 will be presented by each treatment group.

7.4.2.3.9 Change From Baseline in Number of Tablets/Week of Rescue Therapy

Descriptive statistics for actual value and change from baseline in number of tablets/week of rescue therapy at Week 8, 12, and 24 will be summarized by each treatment group.

The number of tablets/week of rescue therapy will be defined as the sum of daily use of rescue therapy over the study days which make up a given study week. The maximum permitted number of tablets per day will be considered as 1, regardless of selected rescue medication. For example, 1 tablet of fexofenadine 60 mg will be converted into 0.5 tablet for standardization as 2 tablets of fexofenadine 60 mg are maximum permitted limit per day.

7.4.3 Quality of Life Analyses

7.4.3.1 Dermatology Life Quality Index

Individual domain scores and overall scores of DLQI will be summarized for baseline and for the actual result and change from baseline by visit for patient with a baseline and the relevant post-baseline visit data. All analyses will be performed based on mITT and PP Sets.

7.4.3.2 Chronic Urticaria Quality of Life Questionnaire

Individual domain and overall raw scores of CU-Q_2oL will be converted to 0 to 100-point scores according to the following formula:

$$[(\text{sum of items} - \text{minimum}) / (\text{maximum} - \text{minimum})] \times 100$$

Individual domain scores and overall score of CU-Q_2oL will be summarized for baseline and for the result and change from baseline by visit for patient with a baseline and the relevant post-baseline visit data. All analyses will be performed based on mITT and PP Sets.

7.4.4 Pharmacokinetic Analyses

Serum concentrations of omalizumab will be summarized using quantitative descriptive statistics (including geometric mean and coefficient of variation, as appropriate) by treatment arm and study visit. Pharmacokinetic parameter of C_{trough} will also be summarized using quantitative descriptive statistics (including geometric mean and coefficient of variation, as appropriate) by treatment and study visit. Graphical presentations of data may be added. All analyses will be performed based on the PK Set.

7.4.5 Safety Analyses

Safety will be assessed through the summary of AEs (including SAEs), AESI, immunogenicity including antidrug antibody and neutralizing antibody, total and free serum IgE, hypersensitivity monitoring, vital signs, body weight, physical examination, clinical laboratory analyses, ECG, pregnancy testing, and prior and concomitant medications throughout the study. These summaries will be produced for the whole study and separately for the each Treatment Period where appropriate. Severity of AEs will be graded according to the CTCAE Version 5.0. All reported terms for AEs and medical history will be coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities. Prior and concomitant medication will be coded to drug class and preferred term using the World Health Organization drug dictionary.

For AESIs, the incidence rate and its difference between treatment arms will be presented along with their 95% CI.

All safety data including immunogenicity will be listed and summarized by treatment arm as appropriate in the Safety Set.

7.4.6 Other Analyses

Demographics (e.g., age, sex, weight, height, body mass index, race and ethnicity), disease-related information and medical history will be presented by means of summary tables (descriptive statistics for quantitative variables, or frequency for qualitative variables).

7.5 Interim Analysis

No interim analyses are planned for this study.

7.6 Data Quality Assurance

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH Good Clinical Practice (GCP) guidelines on quality and risk management.

Step to be taken to ensure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated staff prior to the study, periodic monitoring visits by the Sponsor or its designee, and direct transmission of clinical laboratory data from a central laboratory into the clinical database. The data will be collected via Electronic Data Capture (EDC) using eCRFs. The study center will be responsible for data entry into the EDC system. The eCRF will be reviewed for

accuracy and completeness by the monitor during on-site monitoring visits and after their return to the Sponsor or its designee. In the event of discrepant data, the Sponsor will request data clarification from the study centers, which the study centers will resolve electronically in the EDC system. The Sponsor will be responsible for the data management of this study, including quality checking of the data.

Central Laboratory data and other electronic data (including eDiary) will be sent directly to the Sponsor using their standard procedures to handle and process the electronic transfer of these data. Quality assurance staff from the Sponsor or its designee may visit the study center to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for inspection and comparison with the eCRF. Patient privacy must, however, be respected. Sufficient prior notice will be provided to allow the Investigator to prepare properly for the audit.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a licensing application. The Investigator should immediately notify the Sponsor or its designee if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

8 Investigator's Obligations

The following administrative items are meant to guide the Investigator in the conduct of the study but may be subject to change based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IEC but will not result in protocol amendment.

8.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be disclosed without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the regulatory authorities or the IEC.

The Investigator, all employees, and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

8.2 Independent Ethics Committee

Regulations and the ICH guidelines require that approval be obtained from an IEC before participation of human patients in research studies. Before study onset; the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian, must be approved by the IEC. Documentation of all IEC approvals and of the IEC compliance with ICH harmonised tripartite guideline E6(R2): GCP will be maintained by the study center and will be available for review by the Sponsor or its designee.

All IEC approvals should be signed by the IEC chairman or designee and must identify the IEC name and address, the clinical protocol by title or protocol number or both, and the data approval or a favorable opinion was granted.

The Investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IEC. The Investigator must promptly supply the Sponsor or its designee, the IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing risk to patients.

8.3 Patient Information and Consent

A written informed consent in compliance with the ICH E6(R2) guidelines will be obtained from each patient before entering the study or performing any unusual or non-routine procedure that involves risk to the patient. An informed consent template may be provided by the Sponsor to the study centers. If any institution-specific modifications to study-related procedures are proposed or made by the study center, the consent should be reviewed by the Sponsor or its designee or both before IEC submission. Once reviewed, the consent will be submitted by the Investigator to his or her IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form in case new information becomes available that may be relevant to the patient's willingness to continue participation in the clinical study.

Before recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the ICF.

In addition to the standard requirements that physicians are currently obliged to observe when providing information, the following points must also be covered:

- A description of the objectives of the study and how it will be organized
- The type of treatment
- Any potential negative effects attributable to the study drug
- The freedom to ask for further information at any time
- The patient's right to withdraw from the clinical study at any time without giving reason and without jeopardizing the patient's further course of medical treatment
- The existence of patient insurance coverage and a summary of what is included in this coverage
- Adequate time and opportunity to satisfy questions will be given to the patients.

The Investigator will be supplied with an adequate number of ICFs to be used. The forms will be signed and dated by both the Investigator or Sub-Investigator and the patient's legal representatives (according to the local regulations) before the beginning of the study. The Investigator shall retain

the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

To ensure medical confidentiality and data protection, the signed ICFs will be stored in the Investigator's study file. The Investigator will allow inspection of the forms by authorized representatives of the Sponsor, IEC members, and regulatory authorities. The Investigator will confirm, by signing and dating the eCRFs, that informed consent has been obtained.

8.4 Study Reporting Requirements

By participating in this study, the Principal Investigator or Sub-Investigator agrees to submit reports of SAEs according to the timeline and method outlined in Section 6.4.2.1.7. In addition, the Principal Investigator or Sub-Investigator agrees to submit annual report to his or her IEC as appropriate.

8.5 Financial Disclosure and Obligations

CELLTRION, Inc. is the Sponsor of the study and is funding the study. All financial details are provided in the separate contracts between the institution, Investigator, and [redacted] (CRO). The Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws. The Sponsor will indemnify all Investigators participating in this study against future claims by study patients; the terms of this will be detailed within a separate letter of indemnification. The indemnity will only apply where all study procedures have been carried out according to this protocol.

The Investigator is required to take out liability insurance for all patients included in the study as required by local law and/or regulations and/or ICH guideline for GCP, whichever is applicable.

The Investigator and the Sponsor will sign a clinical study agreement before the start of the study. The agreement will outline overall Sponsor and Investigator responsibilities in relation to the study. Financial remuneration will cover the costs based on the calculated expenses of performing the study assessments in accordance with the protocol and the specified terms of payment will be described in the contract.

Investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements per regional requirements. In addition, the Investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the Sponsor nor its designee is financially responsible for further testing or treatment or any medical condition that may be detected during the Screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor its designee is financially responsible for further treatment of the patient's pre-existing disease prior to study participation (Screening).

The Sponsor undertakes to compensate the patient for injuries which are considered, on the balance of probabilities, to have arisen as a result of their participation in the trial.

8.6 Investigator Documentation

Before beginning the study, the Investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the FDA Code of Federal Regulations by providing the following essential documents, including but not limited to:

- Independent Ethics Committee approval.
- Original Investigator-signed Investigator agreement page of the protocol
- Curriculum vitae for the Principal Investigator and each Sub-Investigator. Current licensure must be noted in the curriculum vitae. The curriculum vitae will be signed and dated by the Principal Investigators and Sub-Investigators at the study start-up, indicating that they are accurate and current
- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements. In addition, the Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study
- Independent Ethics Committee-approved informed consent, samples of study center advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the study center.

8.7 Study Conduct

The Investigator agrees that the study will be conducted according to the Declaration of Helsinki and the principles of ICH E6(R2). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

8.8 Data Collection

8.8.1 Electronic Case Report Forms and Source Documents

It is the intent of this study to acquire study data via electronic format. As part of the responsibilities assumed by participating in the study, the Principal Investigator or Sub-Investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The Principal Investigator or Sub-Investigator agrees to maintain source documentation (e.g., laboratory reports), enter patient data into the eCRF as accurately as possible, and respond to any reported discrepancies rapidly. These source documents may include diaries, laboratory reports, ECG strips, etc. For data collected using [redacted] electronic clinical outcome assessment system, data in this system itself will be considered as source document.

The eCRF are accessed through the appropriate system, which allows for on-site data entry and data management. Study center users will have access to read and write in the Sponsor's database where the clinical data are collected. This provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling study center coordinators to resolve and manage discrepancies in a timely manner.

Each study center staff involved with the study at each study center will have an individual logon account and password that allow for record traceability. Thus, the system and subsequently any investigative reviews, can identify coordinators, Investigators and individuals who have entered or modified records.

8.9 Adherence to Protocol

The Investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

8.10 Investigator's Final Report

Upon completion of the study, the Investigator, where applicable, should inform the institution; the Investigator/institution should provide IEC with a summary of the study's outcome and the Sponsor and regulatory authority(ies) with any reports required.

8.11 Record Retention

All correspondence (e.g., with Sponsor, IEC, or Clinical Research Associates) relating to this clinical study will be kept in appropriate file folders. Records of patients, source documents, eCRFs, and drug inventory sheets pertaining to the study must kept on file.

Essential documents should be retained until at least 15 years after completion or discontinuation of the trial or at least 2 years after the granting of the last marketing authorization in the EU (when there are no pending or contemplated marketing applications in the EU) or for at least 2 years after formal discontinuation of clinical development of the IP, whichever is the longest.

These documents can be retained for a longer period, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

If an Investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person, who will accept the responsibility. Notice of transfer must be made to and agreed upon by the Sponsor.

8.12 Patients Identification Register

The Investigator agrees to complete a patient identification register. This form will be treated as confidential and will be filed by the Investigator in the Study Center Master File. Otherwise, all reports and communications relating to the study will identify patients by assigned number only.

8.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the Investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor, but data publication thereof will not be unduly withheld.

9 Study Management

9.1 Sponsor

CELLTRION, Inc.

[redacted]

Sponsor Representative

[redacted]

9.2 Vendor Contact

CRO

[redacted]

SAE Reporting

[redacted]

9.3 Central Analytical Facilities

Any analytical facilities and procedures utilized for this study must be Good Laboratory Practice compliant. Details of analytical facilities are presented in the ICF.

9.4 Monitoring

9.4.1 Data Safety Monitoring Board

This study will be monitored by an independent DSMB consisting of a PK specialist, statistician, chairing physician, and an independent physician. The DSMB will review and evaluate

accumulating safety data to ensure the safety of study patients and also review study results when the CSR is available.

Further details will be provided in the independent DSMB charter.

9.4.2 Monitoring of the Study

The clinical monitor, as a representative of the Sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the Investigator and study center at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff. In case where a monitoring visit cannot be made because of the pandemic situation of COVID-19 the monitor will discuss with the Sponsor, CRO, and the Investigator for further plan, which will be specified in Appendix 2.

All aspects of the study will be carefully monitored, by the Sponsor or its designee, for compliance with applicable government regulation with respect to current ICH E6(R2) and SOPs.

9.4.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, or a regulatory agency to access to all study records.

The Investigator should promptly notify the Sponsor and [redacted] of any audits scheduled by any regulatory authorities.

9.5 Management of Protocol Amendments and Deviations

9.5.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the Sponsor or its designee. Substantial amendments to the protocol must be submitted in writing to the applicable IEC and Regulatory Authority for approval before patients are enrolled under an amended protocol. This will be fully documented.

The Investigator must not implement any deviation from or change to the protocol without discussion and agreement from the Sponsor or its designee, and prior review, documented approval, and favorable opinion of the amendment from the relevant IEC and/or regulatory authorities, except where it is necessary to eliminate an immediate hazard to patients or where the changes involve only logistical or administrative aspects of the clinical study. The eCRF and source documents will describe any departure from the protocol and the circumstances requiring it.

Protocol amendments will be submitted to the appropriate authorities as required by the applicable regulatory requirements.

9.5.2 Protocol Deviations

The Investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IEC for review and approval, to the Sponsor for agreement and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IEC and agreed to by the Investigator. A significant deviation occurs when there is non-adherence to the protocol by the patient or Investigator that results in a significant and additional risk to the patient's right, safety and well-being. Significant deviations may include non-adherence to inclusion or exclusion criteria, or non-adherence to regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Deviations will be defined before unblinding. Principal Investigators will be notified in writing by the monitor of deviations. Protocol deviations will be notified to IEC according to their regulations.

9.6 Study Termination

Although the Sponsor has every intention of completing the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date of the final CSR generated.

9.7 Final Report

Whether the study is completed or prematurely terminated, the Sponsor will ensure that the CSRs are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The Sponsor will also ensure that the CSRs in marketing applications meet the standards of the ICH harmonized tripartite guideline E3: Structure and content of CSRs.

The Sponsor plans to prepare 2 CSRs to report the following:

- First CSR: data for each patient up to Week 24
- Final CSR: all data after completion of the study

If additional CSRs are required for regulatory or academic purposes, CSRs will be generated after the first database lock and unblinding process.

10 Reference List

Abdelmaksoud Ayman, Mohamad Goldust, and Michelangelo Vestita. Omalizumab and COVID-19 treatment: Could it help? Dermatologic Therapy 2020;33(4):e13792. doi:10.1111/dth.13792.

American College of Allergy, Frequently Asked Patient Questions About the COVID-19 Vaccine, 14 May 2021. Available from: https://acaai.org/news/frequently-asked-patient-questions-about-covid-19-vaccine

Baiardini I, Pasquali M, Braido F, *et al.* A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-Q2oL). *Allergy.* 2005;60:1073–78.

Canadian Society of Allergy and Clinical Immunology, COVID-19 Vaccines FAQ, 09 June 2021. Available from: https://csaci.ca/covid-19-vaccines-faq/

Casale TB, Bernstein JA, Maurer M et al. Similar efficacy with omalizumab in chronic idiopathic/spontaneous urticaria despite different background therapy. *J Allergy Clin Immunol Pract.* 2015;3:743-50.

Criado, Paulo Ricardo, et al. What the physicians should know about mast cells, dendritic cells, urticaria, and omalizumab during COVID-19 or asymptomatic infections due to SARS-CoV-2? Dermatologic Therapy 2020:e14068. doi: 10.1111/dth.14068.

European Medicines Agency. (2014). Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014.

European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). (2005). Xolair Scientific Discussion. Available from: https://www.ema.europa.eu/en/documents/scientific-discussion/xolair-epar-scientific-discussion_en.pdf

European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). (2012). Guideline on similar biological medicinal products containing monoclonal antibodies–non-clinical and clinical issues. London. EMA/CHMP/BMWP/403543/2010. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-monoclonal-antibodies-non-clinical_en.pdf

European Medicines Agency. Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic. Version 4. 04 February 2021. Available from: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

FDA Code of Federal Regulations Title 21 (regulation 21 CFR 320.38). (2020). Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.38

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)-a simple practical measure for routine clinical use. *Clin Exp Dermatol.* 1994;19:210-6.

Food and Drug Administration (FDA), Department of Health and Human Services (US). (2015). Guidance for Industry: Scientific considerations in demonstrating biosimilarity to a reference product. FDA. Available from: https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf

Food and Drug Administration (FDA). (2014). Clinical Pharmacology review. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/103976Orig1s5211.pdf

Hogan II, Reed B., et al. Dual-histamine receptor blockade with cetirizine-famotidine reduces pulmonary symptoms in COVID-19 patients. Pulmonary Pharmacology & Therapeutics. 2020;63:101942. doi:10.1016/j.pupt.2020.101942.

Humphreys F, Hunter JAA. The characteristics of urticaria in 390 patients. *Br J Dermatol*. 1998;138:635-8.

ICH Assembly. (2016). Integrated Addendum to ICH E6(R2): Guideline for good clinical practice E6(R2): ICH harmonised guideline. International Council for Harmonisation.

Johansson, S. G. O., Tari Haahtela, and Paul M. O'Byrne. Omalizumab and the immune system: an overview of preclinical and clinical data. Annals of Allergy, Asthma & Immunology. 2002;89(2):132-138. doi:10.1016/S1081-1206(10)61928-X.

Kaplan AP. Chronic urticaria: pathogenesis and treatment. *J Allergy Clin Immunol.* 2004 Sep;114(3):465-74.

Mathias SD, Crosby RD, Zazzali JL, Maurer M, Saini SS. Evaluating the minimally important difference of the urticaria activity score and other measures of disease activity in patients with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol*. 2012;108:20-4.

Maurer M, Altrichter S, Bieber T, *et al.* Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol*. 2011;128(1):202-9.e5.

Maurer M, Rosen K, Hsieh HJ, *et al.* Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med.* 2013;368(10):924-35.

Pfaar O, Klimek L, Hamelmann E, *et al.* COVID-19 vaccination of patients with allergies and type-2 inflammation with concurrent antibody therapy (biologicals) – A Position Paper of the German Society of Allergology and Clinical Immunology (DGAKI) and the German Society for Applied Allergology (AeDA). *Allergologie select.* 2021;5:140-147. doi: 10.5414/ALX02241E

Recalcati, S. Cutaneous manifestations in COVID-19: a first perspective. Journal of the European Academy of Dermatology and Venereology. 2020;34(5):e212-e213. doi:10.1111/jdv.16387.

Roh JY. Updated treatment guideline of chronic spontaneous urticaria. *J Korean Med Assoc.* 2019;62(1):37-46.

Saini SS, Bindslev-Jensen C, Maurer M, *et al.* Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: A randomized, placebo-controlled study. *J Invest Dermatol.* 2015;135(1):67-75.

Sampson HA, Muñoz-Furlong A, Campbell RL, *et al.* Second symposium on the definition and management of anaphylaxis: Summary Report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. *J Allergy Clin Immunol.* 2006;117:391-7.

US Department of Health and Human Services. (2017). National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

World Health Organization. Disease outbreak news. 04 October 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20201005-weekly-epi-update-8.pdf

World Health Organization. Q&A on coronaviruses (COVID-19). 13 May 2021. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-coronaviruses

World Health Organizations (WHO). (2010). Expert Committee on Biological Standardization. Guidelines on evaluation of similar biotherapeutic products. Available from: https://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

Xolair (omalizumab) [Prescribing information]. Genentech, Inc. South San Francisco (CA) USA; 04/2021.
Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103976s5238lbl.pdf

Xolair (omalizumab) [Summary of product characteristics]. Novartis Europharm Ltd. Elm Park, Ireland; 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/xolair-epar-product-information_en.pdf

Zuberbier T, Balke M, Worm M, Edenharter G, Maurer M. Epidemiology of urticaria: a representative cross-sectional population survey. *Clini Exp Dermatol*. 2010;35:869–73.

Zuberbier T, Aberer W, Asero R, *et al.* The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73:1393-414.

11 Appendices

Appendix 1. Schedule of Assessments

Procedure	Screening	Treatment Period I			Treatment Period II			EOT	Follow-up Period			EOS
Week		**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**
Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**
Window			**± 3**	**± 3**	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Screening												
Informed consent	X											
Demographic data	X											
Medical history	X											
Stool and parasite evaluation[1]	X											
Viral serology[2]	X							(X)				(X)
Inclusion/Exclusion Criteria	X	X[4]										
C3, C4, and total hemolytic complement (CH_{50})[3]		X[4]										
Randomization[5]		X[4]			X[4]							
Study Treatment												
Study drug (CT-P39 or Xolair) /placebo administration[6]		X	X	X	X	X	X					
Hypersensitivity/allergic reactions and injection site reaction monitoring[7]		X	X	X	X	X	X					
Patient Reported Outcomes/Efficacy												
Patient eDiary[8]	X	X										
Patient Reported Outcomes/QoL												
CU-Q_2oL		X[4]			X[4]			X				X
DLQI		X[4]			X[4]			X				X
Immunogenicity/PK Sampling												
Immunogenicity sampling[9]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X				X
Pharmacokinetic sampling[10]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X				X
Safety/Laboratory Test												
Vital signs	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	X	X	X	X
12-lead ECG	X	X[4]			X[4]			X				X
Weight and height[11]	X	X[4]			X[4]			X				X

Procedure	Screening	Treatment Period I			Treatment Period II			EOT	Follow-up Period			EOS
Week		**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**
Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**
Window			**± 3**	**± 3**	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Physical examination	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	X	X	X	X
Hematology	X				X[4]			X				X
Clinical chemistry	X				X[4]			X				X
Urinalysis	X				X[4]			X				X
Total and free IgE		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X				X
Pregnancy test (serum)[12]	X											X
Pregnancy test (urine)[12]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X				
Prior and concomitant medications[13]	X	X										
Adverse event monitoring[14]	X	X										

Abbreviations: CU-Q_2oL = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eDiary = electronic diary; EOS = end-of-study; EOT = end-of-treatment; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HIV = human immunodeficiency virus; HSS = hives severity score; ISS7 = weekly itch severity score; PK = pharmacokinetics; QoL = quality of life; UAS = urticaria activity score; UAS7 = weekly urticaria activity score; ULN = upper limit of normal.

Note: Patients who discontinue the study drug during any of treatment periods will return to the study center by regular scheduled time intervals for planned clinical assessments. If a patient withdraws from the study, the last visit will be considered as the EOS visit and the all assessments planned for the EOS visit should be performed. Otherwise, a patient will be required to attend for the regularly scheduled EOS visit.

1. Stool ova and parasite examination should be performed on patients with an absolute eosinophil count > 2 × ULN at Screening AND risk factors for parasitic disease listed at the exclusion criterion #5.
2. Viral serology tests will be performed for HBsAg, HBsAb, hepatitis B core antibody, hepatitis C antibody, and HIV-1 and -2 in all patients (mandatory). For patients who were enrolled based on the HBV DNA test, testing of HBsAg, HBsAb, and HBV DNA will be performed at EOT (Week 24) and EOS visits.
3. Complement (C3 and C4) and total hemolytic complement (CH_{50}) will be assessed on Day 1 prior to the study drug administration. In case of allergic reaction type III, including serum sickness/serum sickness-like reactions (e.g., arthritis/arthralgias, rash, fever, lymphadenopathy), additional complement (C3 and C4) and total hemolytic complement (CH_{50}) assessment will be performed.
4. For study drug administration visit, procedures will be performed prior to the study drug administration.
5. Patients will be randomly assigned to receive 300 mg of CT-P39, 300 mg of Xolair, 150 mg of CT-P39, or 150 mg of Xolair on Day 1 (Week 0) prior to the study drug administration. Second randomization will be performed prior to the study drug administration on Week 12.
6. If dose delay of more than 1 week or missed dose is expected, it should be discussed with Sponsor or its designee regarding the patient's eligibility to continue study treatment.

7. Additional vital signs including blood pressure, heart and respiratory rates, and body temperature (prior to the study drug administration (within 30 minutes) and 1 hour (± 10 minutes) after subcutaneous injection) will be monitored for possible hypersensitivity reactions. In addition, hypersensitivity will be monitored by routine continuous clinical monitoring, including patient-reported signs and symptoms. In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available; in addition, any type of ECG can be performed at the Investigator's discretion. If the patient experiences any of hypersensitivity signs and symptoms after discharge, the patient can visit the study center for further assessment. The diagnostic assessment such as serum samples for C3, C4, and total hemolytic complement (CH_{50}) can be ordered based on the Investigator's discretion. Injection site reactions will be assessed 30 minutes (± 10 minutes) after the end of the study drug administration.
8. The patient eDiary includes UAS (ISS and HSS), angioedema episodes, and rescue medication use. The patient eDiary will be given to patients at the first of Screening visit and completed twice daily by each patient. During the Screening Period, a patient should complete the patient eDiary including UAS (ISS and HSS) twice daily for 7 consecutive days (Day -7 to Day -1) prior to the first study drug administration as per inclusion criteria #3-b and #4.
9. Additional immunogenicity will be assessed when immune-related AE occurs.
10. If a patient discontinues the study drug during treatment period, the blood sample for PK assessments should be collected only at the right next scheduled visit of the last study drug administration visit and EOS visit.
11. Height will be measured only at the Screening.
12. For women of childbearing potential, a serum pregnancy test will be conducted at Screening and EOS visit. Urine pregnancy test will be performed prior to the study drug administration during all Treatment Period visits and EOT (Week 24) visit and any time if pregnancy is suspected. If a urine pregnancy test result is found equivocal or positive, a confirmatory serum pregnancy test will be performed.
13. All medications used during the study, as well as all medications taken within 30 days of the first study drug administration on Day 1 (Week 0) and until EOS visit will be collected (inclusive of the applicable periods for prohibited medications as defined in Section 5.6).
14. Adverse events will be assessed from the date the informed consent form is signed until up to EOS visit, regardless of the relationship to the study drug. After the EOS visit, serious adverse drug reaction will be reported to the Sponsor or its designee.

Appendix 2. Risk Assessment and Mitigation Plan due to COVID-19

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially identified during an outbreak of atypical viral pneumonia cases of unknown cause in the People's Republic of China in December 2019 and the disease caused by SARS-CoV-2 has been designated as COVID-19. On 11 March 2020, World Health Organization (WHO) declared the SARS-CoV-2 infection outbreak a global pandemic as there are now in excess of 1 million deaths have been reported globally (WHO disease outbreak news, 2020).

Due to the global impact of the COVID-19 pandemic, the Sponsor is taking proactive measures to guarantee that all site staff and patients involved in trial are secure and the patients remain in the study until their last visit, with continuation of treatment during study period.

1. Benefit and Risk Assessment on Study Population

Considering the most common symptoms of COVID-19 are fever, dry cough, and tiredness (WHO Q&A on coronaviruses [COVID-19]) and the irrelevance between cause of COVID-19 and CSU disease itself, CSU symptoms and disease itself have low chance to be deteriorated directly due to COVID-19. However, the irrelevance cannot be concluded since there are no studies conducted and there were few cases reporting cutaneous eruptions and itching as symptoms of COVID-19 (Sebastiano Recalcati, 2020).

In regards to the effect of omalizumab on immune system, Committee for Medicinal Products for Human Use stated no signs of immune-complex disorders or autoimmune disorders were found and an immunosuppressive effect of omalizumab was the only likely situation in which the malignancies would progress rapidly in relation to treatment with omalizumab (EMA 2005). Furthermore, one previous article clearly stated that inhibition of IgE activity through treatment with omalizumab has not been associated with any other adverse impact upon the immune system or other body systems while any complications resulting from reduction in circulating free IgE might be expected in theory (Johansson *et al.,* 2002).

Cells that express FcεRIα, including mast cells, basophils, and dendritic cells, are regulated by IgE binding to FcεRIα. Omalizumab binds IgE and prevents its engagement with FcεRIα, thereby downregulating its expression and modulating cell function. Recent studies on omalizumab demonstrate that it can ameliorate the inadequate antiviral response observed in patients with allergic asthma. Children with severe asthma are more susceptible to virus-induced asthma exacerbations, particularly those with higher serum IgE levels (Criado *et al.,* 2020). Also, a recent

study on omalizumab demonstrates the reduction of local nasal mucosal inflammation, improvement of nasal respiration and sino-nasal function in patients with chronic rhinosinusitis (Abdelmaksoud *et al.,* 2020). Omalizumab decreased the duration of human rhinovirus infections, viral shedding, and risk of rhinovirus-related illnesses compared with guideline-driven care alone. Omalizumab attenuated dendritic cell FcεRIα protein expression while simultaneously augmenting IFN-α responses to rhinovirus and influenza virus. These findings provide direct evidence that blocking IgE decreases susceptibility to respiratory viral illnesses through enhanced IFN-α responses denoting an antiviral potential of omalizumab (Criado *et al.,* 2020).

Moreover, there has yet to be concluded that antihistamines, which is a protocol defined combination treatment, can effectively treat COVID-19, currently, it is shown that cetirizine provides proof-of-concept of a safety and effective method to reduce the progression in symptom severity, presumably by minimizing the histamine-mediated cytokine storm (Hogan *et al.,* 2020).

Taking all these facts into consideration, the risks for each patient are not expected to increase by participating in this study. A systematic risk assessment will be conducted during the study by the Sponsor through a diligent interactions with the Investigators and DSMB.

2. Mitigation Plans

Investigational Product Management

To better cope with the sudden imposition of movement restriction and/or increase shipment lead time due to frequent flight cancellation and limited staff at customs, sufficient IP will be supplied to cover patient visit for longer period. Inter-country IP transfer using regional airways will be considered in case intercontinental flights are repeatedly cancelled. In addition, Sponsor will prepare site-to-site transfer of IP from nearby clinical sites in case agile resupply is required (e.g., patients are enrolled in a site more than anticipated but additional supplied IP could not be sufficient).

Rescheduling of Visit and Study Drug Administration Schedule of Patients

The COVID-19 screening tests will be performed locally based on each site and/or local regulatory guidelines upon the Investigator's discretion throughout the study period. If COVID-19 is confirmed positive during the Screening Period, the patient should not be enrolled in this study until confirmation of complete recover from COVID-19 as per site and/or local regulatory guidelines. Although patients can be rescreened only once in normal circumstance as specified in Section 4.2.1, additional rescreening can be performed only in limited cases considering

COVID-19. If COVID-19 is confirmed after randomization, the Investigators will discuss on a case-by-case basis regarding the specific case of the patient with the Sponsor. In case of patient who has contact with COVID-19 patients within 14 days from any site visit, Investigator will reconsider the enrollment or visit schedule following the site and/local regulatory guidelines.

Investigators will promptly notify the Sponsor if any unfavorable situation has occurred in relation to local COVID-19 status (e.g., site shut down, lock down of city, cohort isolation, etc.). For sites where the patients are unable to travel or use public transportation, the Sponsor will support the patients with alternative transportation or reimbursement for travel to ensure the visits can be made within the window or the visit can be proceeded at the earliest.

Study drug should be administered preferably within 1 week from the planned dosing date, however, if dose delay of more than 1 week or missed dose is expected, whether to continue with the subsequent study treatment will be discussed with the Sponsor, ensuring the compliance with the trial protocol to such an extent that an ongoing benefit-risk assessment for the clinical trial and patients is still possible. Even though the study drug cannot be administered on the scheduled time point, patients will keep taking protocol defined H_1-antihistamines as planned.

Even if the study visit cannot be made, patient reported outcomes, such as Urticaria Activity Score (itch severity and hives severity scores), angioedema episode, and rescue medication information, will be continuously collected via patient eDiary and other data will be collected via phone call and during the next visit, if possible. Investigator will keep following up with patients regarding any safety issues by phone call before the patients visit the site.

Although the COVID-19 pandemic situation is likely to introduce more protocol deviations than normal circumstance, protocol deviations will be managed in accordance with the standard procedures. The number and type of deviations will be monitored periodically to assess whether a protocol amendment or other modifications are needed.

Site Monitoring and Audit

In case where a monitoring visit cannot be made because of the situation of COVID-19, centralized monitoring will be performed by the Sponsor and/or CRO as alternatives particularly, for the sites where the first patient is randomized but the first monitoring visit is not performed. Manual data review on eCRF will be performed and if any mistakes or deviations are observed, proper guidance will be provided to avoid them in the future. Sponsor and/or CRO will review the data entered in eCRF continuously and ensure raising queries and support the sites as necessary. If necessary,

Sponsor will create and review a report based on the eCRF data to check whether visits, assessments and administrations of study treatment are in progress according to protocol and the same will be shared with CRO for site management.

Audits are needed as part of implementing quality assurance throughout the study period in order to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements. In case where an audit cannot be made due to COVID-19 pandemic situation, Sponsor will postpone audits or consider the remote audits after careful consideration of COVID-19 pandemic situation according to *Guidance on the management of clinical trials during the COVID-19 (coronavirus) Pandemic* (EMA 2021). Audits will be conducted only when permitted under national, local and/or organizational social distancing restrictions.

Handling of Missing Data

To assess any possible risks on data collection, data will be routinely reviewed according to Centralized monitoring plan and Risk based monitoring plan. After data collection, missing data on the primary analysis due to COVID-19 will be handled equally as specified in Section 6.1.2 as other missing cases. However, if a different approach is required for missing data due to COVID-19, it will be discussed at the blinded data review meeting on a case-by-case manner and method of handling missing data will be specified in the SAP.

3. COVID-19 Vaccination

At present, two mRNA-based vaccines (Comirnaty from BioNTech/Pfizer and Spikevax from Moderna) and two vector-based vaccines (Vaxzevria from AstraZeneca and COVID-19 Vaccine from Johnson & Johnson) have been approved by the EMA and Ministry of Food and Drug Safety of South Korea, and in addition, an inactivated-virus vaccine (Coronavac from Sinovac Biotech) has been approved in Ukraine. There are several COVID-19 vaccine candidates under rolling review. According to a position paper published from the German Society of Allergology and Clinical Immunology and the German Society for Applied Allergology (Pfaar *et al.*, 2021), patients with CSU have no increased risk of allergic reactions to COVID-19 vaccinations, despite vaccination may result in transient exacerbation due to general immune stimulation. Other academies of allergy are also taking similar position (AAAAI Ask the expert, 2021; CSACI frequently asked questions, 2021).

As there are no known potential interactions between COVID-19 vaccine and omalizumab, academies of immunology are informing that patients treated with omalizumab can be vaccinated. However, there are no standardized recommendations on intervals between

vaccination and omalizumab, and it varies from at least 1 day to 1 week apart (AAAAI Ask the expert, 2021; CSCAI frequently asked questions, 2021; Pfaar *et al.*, 2021). If a patient has plan to get COVID-19 vaccine during the study, COVID-19 vaccine should not be injected on the same day as an administration of the study drug at least, and it is recommended to have a time-lag of at least 1 week after the previous or at least 1 week before the next study drug administration to make it distinguishable what caused an AE if the patient has an AE during the study after vaccination.