CELLTRION Inc.
CT-P39 3.1

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

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Statistical Analysis Plan

Version 1.1 (A)

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Upon review of this document, including table, listing and figure shells, the undersigned approves the final statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing and figure production can begin.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug Antibody
AE(s)	Adverse Event(s)
AESI(s)	Adverse Event(s) of Special Interest
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BLQ	Below Lower Limit of Quantification
BP	Blood Pressure
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
C_{trough}	Trough Serum Concentration
CU-Q_2oL	Chronic Urticaria Quality of Life Questionnaire
CV%	Percent Coefficient of Variation
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic Acid
DRM	Data Review Meeting
ECGs	Electrocardiograms
eCRF	electronic Case Report Form
eDiary	electronic Diary
EOS	End-of-Study
EOT	End-of-Treatment
GCP	Good Clinical Practice
HBcAb	Hepatitis B core Antibody
HBsAb	Hepatitis B surface Antibody
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCAb	Hepatitis C Antibody
HIV	Human Immunodeficiency Virus
HSS	Hives Severity Score
HSS7	Weekly Hives Severity Score
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IgE	Immunoglobulin E
ISR	Injection Site Reactions
ISS	Itch Severity Score
ISS7	Weekly Itch Severity Score

Abbreviation	Definition
IWRS	Interactive Web Response System
LLoQ	Lower Limit of Quantification
MI	Multiple Imputation
MID	Minimally Important Difference
mITT	modified Intent-to-Treat
MAR	Missing at Random
MNAR	Missing Not at Random
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing Antibody
PFS	Pre-filled Syringe
PK	Pharmacokinetic(s)
PP	Per-protocol
PT	Preferred Term
QoL	Quality of Life
RAN	Randomized
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SI	System International
SOC	System Organ Class
TEAE(s)	Treatment-emergent Adverse Event(s)
TESAE(s)	Treatment-emergent Serious Adverse Event(s)
TP2	Treatment Period II
UAS	Urticaria Activity Score
UAS7	Weekly Urticaria Activity Score
ULoQ	Upper Limit of Quantification
USA	United States of America
WHO	World Health Organization

1 ADMINISTRATIVE STRUCTURE

This study is being conducted under the sponsorship of CELLTRION, Inc. (hereinafter referred to as "CELLTRION"). The clinical monitoring and medical writing are being performed under contract with [redacted], in collaboration with CELLTRION. The randomization is being performed under contract with [redacted]. The data management and statistical analyses including pharmacokinetics (PK) parameter analysis are being performed by CELLTRION.

2 INTRODUCTION

This Statistical Analysis Plan (SAP) defines the statistical methods for the analysis and presentation of data from CELLTRION study numbered CT-P39 3.1, entitled as "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".

There are two clinical study reports (CSRs) planned for the following time points:

- 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 database lock and unblinding process.

This SAP covers all specified analyses and is based on the following documents:

- Study Protocol Version 2.3 A.0 – 10th August 2021
- Unique Case Report Form Version 2.0 – 24th March 2022

Table, Listing and Figure mock shells will be provided as an addendum to this document.

2.1 Data Cut-off for Analysis

The first CSR will include all analysis results, using data up to end-of-treatment (EOT) (Week 24) of each patient. For the data that are monitored continuously, the data of which start date is on or before EOT will be included. If there is no EOT visit, the planned EOT (expected Week 24 visit calculated from the first treatment visit date) will be used instead for patients who have entered Follow-up Period or all collected data will be included for patients who have terminated the study participation before entering Follow-up Period.

For electronic diary (eDiary) data which is collected daily including urticaria activity score (UAS) (itch severity score [ISS] and hives severity score [HSS]), angioedema episodes and rescue medication, the data collected up to Day 168 will be included.

The final CSR will include all analysis results collected up to the completion or termination of all patients from the study.

3 STUDY OBJECTIVES

3.1 Primary Objectives

- To demonstrate the equivalence of CT-P39 to Xolair at a dose of 300 mg in terms of efficacy in patients with 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

3.2 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, quality of life (QoL), safety, and immunogenicity of CT-P39 and Xolair

4 OVERALL STUDY DESIGN AND PLAN

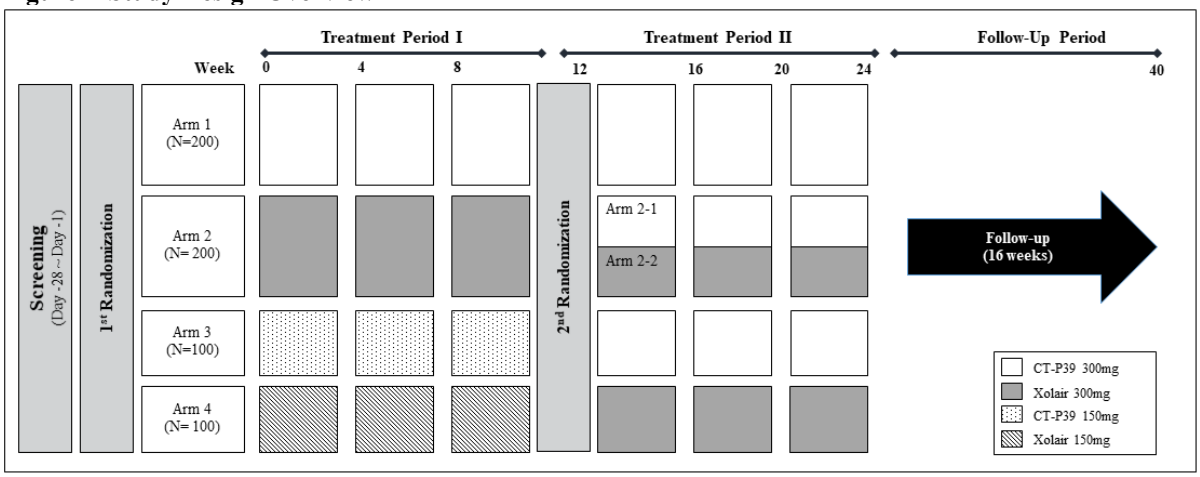
This is a double-blind, randomized, active-controlled, parallel group, multicenter, Phase 3 study to evaluate the efficacy and safety of CT-P39 compared with Xolair, when subcutaneously administered as an add-on therapy for the treatment of patients with CSU who remain symptomatic despite an approved 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: Screening Period of 4 weeks, 2 Treatment Periods of 12 weeks each, and a Follow-up Period of 16 weeks.

Details of each visit and assessment that will be performed at each time point are specified in the schedule of assessments (Appendix 1). For the effect of treatment policy, patients will continue to be followed for all regularly scheduled visits to have efficacy and safety assessments, even after treatment discontinuation and use of rescue therapy.

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

Figure 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.

5 GENERAL STATISTICAL CONSIDERATIONS

Continuous data will be summarized using descriptive statistics: number of subjects (n), mean, standard deviation (SD), minimum, median, and maximum, unless otherwise specified. The descriptive statistics will be calculated using raw data before rounding although rounded values are listed. The following rules will be considered regarding the number of decimal places:

- Minimum and maximum will be presented to the same number of decimal places as reported.
- Mean, median, geometric mean, and SD will be rounded to one more decimal place than the maximal decimal place of values in the source listing.
- Percent coefficient of variation (CV%) will be displayed to one decimal place.
- Point estimate and its confidence interval (CI) obtained will be displayed to two decimal places.

Geometric mean will not be reported if the dataset includes zero values and CV% will not be reported if the mean is zero.

Categorical data will be summarized using frequency tables showing numbers and percentages of patients. Percentages will be rounded to one decimal place and will be suppressed when the count is zero. A row denoted “Missing” will be included in count tabulations where necessary to account for missing values. The denominator for all percentages will be the number of patients within each treatment group for the population of interest, unless otherwise specified.

Unscheduled visit will not be summarized in visit-based tables, unless otherwise specified. However, all data will be displayed in listings. Unless otherwise specified, listings will be sorted by treatment group, patient number and visit, if applicable. In cases where more ordering is required, other variables will be included in the sort order as applicable.

For the purpose of summarization, any numeric values recorded below the lower limit or above the upper limit of quantification will be set to the respective limit for all related summaries unless otherwise specified. In listings, original results containing inequality sign will be displayed.

When combining data from eCRF and analytical facilities such as Central Laboratory, discrepancy will be handled as following:

1) Recorded as sample collected in eCRF but no corresponding results from analytical facility – listing will display only sample collection visit/date from eCRF;
2) No corresponding records in eCRF for results from analytical facility – listing will display only specimen collection visit/date and results from analytical facility;
3) Discrepancy in sample collection date from eCRF and analytical facility – listing will display results from analytical facility and visit/date from eCRF; if sample collection date is missing in eCRF then use specimen collection visit/date from analytical facility.

All available results from analytical facilities will be included in the summary table.

This SAP could be updated after the blinded Data Review Meeting (DRM) but prior to database lock to document any changes.

5.1 Software

All statistical analyses and PK parameter calculations will be conducted using Statistical Analysis System (SAS®) software (SAS Institute Inc., Cary, North Carolina, United States of America [USA]) Version 9.4 or higher.

5.2 Sample Size

Sample size was derived based on a power analysis using PASS (version 16.0, NCSS Statistical Software, LLC. Utah, USA). 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 this 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 dose arms (100 patients in each of CT-P39 [Arm 3] and 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 [Arm 3 and Arm 4] and 400 patients for 300 mg dose arms [Arm 1 and Arm 2]) achieves an approximately 97% statistical power to demonstrate similarity using the relative potency of CT-P39 to Xolair using a predefined margin of [0.5, 2.0].

5.3 Randomization, Stratification, and Blinding

An interactive web response system (IWRS) will be used for randomization. Unblinded biostatisticians will generate the randomization schedule for IWRS, which will link sequential patient randomization numbers to treatment arms. Patients will be randomly assigned on Day 1 (Week 0) to receive 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) using a 2:2:1:1 allocation ratio. The randomization to treatment assignment will be stratified by the following:

• Baseline ISS7 (< 13 points versus ≥ 13 points)

• Body weight on Day 1 (< 80 kg versus ≥ 80 kg)

• Country

Patients will receive 3 doses of study drug every 4 weeks up to Treatment Period I (Week 12). 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. For the second randomization, patients who are initially randomized to 300 mg of Xolair (Arm 2) 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 receiving 300 mg of Xolair. Patients who have received 300 mg of CT-P39 (Arm 1) during Treatment Period I will maintain receiving 300 mg of CT-P39. Patients who have received 150 mg of CT-P39 (Arm 3) or Xolair (Arm 4) will maintain the assigned study drug with an increased dose of 300 mg.

The second randomization will be stratified by the following:

• Decrease from baseline in ISS7 at Week 12 (< 5 points versus ≥ 5 points)

• Body weight at Week 12 (< 80 kg versus ≥ 80 kg)

This study will be double-blind. To minimize the risk of unblinding, the study drug will be administered by predefined unblinded site personnel. The unblinded personnel who are responsible for the randomization or administration of study drugs will be predefined within the sponsor and contract research organization (CRO) and not permitted to conduct any patient assessments.

Also, to maintain the study blind between two dose levels (300 mg versus 150 mg) for patients who receive one (150 mg) injection of study drug, an additional placebo injection via pre-filled syringe (PFS) of 1mL solution will be administered.

The blind should be broken during the study only if specific emergency treatment would dictate as knowing the study drug assignment is required for medical management. The date, time, and reason for the unblinding must be documented in the appropriate field of the eCRF and will be listed along with information on patient disposition.

The first code break will occur after database lock for data up to Week 24 for all patients. The second code break will occur after database lock for all data after study completion. The study will remain blinded to the Investigators, patients, CRO and sponsor blinded members until all patients have completed the study and the database has been finalized for study termination.

5.4 Analysis Sets

Definition of each analysis set is described following section. Since there are two randomizations, analysis subsets for Treatment Period II formed after second randomization are defined separately.

- **Randomized (RAN) Set**
  The RAN 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).

- **Randomized Set-Treatment Period II (RAN-TP2) Subset**
  The RAN-TP2 Subset is defined as all patients in RAN Set who underwent the second randomization regardless of whether they received either of the study drugs during Treatment Period II.

- **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 Treatment Period I.

- **Modified Intent-To-Treat Set-Treatment Period II (mITT-TP2) Subset**
  The mITT-TP2 Subset is defined as all patients in mITT Set who underwent the second randomization and receive at least one full dose of either of the study drugs during Treatment Period II.

- **Per-Protocol (PP) Set**
  The PP Set is defined as all randomly assigned patients who receive all 3 doses of study drug during Treatment Period I and have an ISS7 assessment at Week 12.
  Patients with a 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 a case-by-case manner at the blinded DRM held in accordance with International Council for Harmonisation (ICH) harmonised tripartite guideline E9.

- **Pharmacokinetic (PK) Set**
  The PK Set is defined as all patients who receive at least one full dose of either of the study drugs during 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 non-compliant with respect

to dosing, a determination of PK Set will be made on a case-by-case manner at the blinded DRM.

- **Pharmacokinetic Set-Treatment Period II (PK-TP2) Subset**
  The PK-TP2 Subset is defined as all patients in PK Set who receive at least one full dose of either of the study drugs during Treatment Period II and have at least one post-treatment PK result after Week 12.

- **Safety Set**
  The Safety Set is defined as all randomly assigned patients who receive at least one dose (full or partial) of either of the study drugs.

- **Safety Set-Treatment Period II (Safety-TP2) Subset**
  The Safety-TP2 Subset is defined as all patients in Safety Set who receive at least one dose (full or partial) of either of the study drugs during Treatment Period II.

The following analysis sets are primary sets: RAN, mITT, PP, PK, and Safety Sets.

For summaries for primary sets, patients will be analyzed using “CT-P39 300 mg”, “Xolair 300 mg”, “CT-P39 150 mg or Dose increase”, and “Xolair 150 mg or Dose increase” groups according to the treatment to which they were initially randomized. For PK and Safety Sets, patients will be analyzed using above four groups but according to the actual treatment they received in Treatment Period I. If there is a patient with such a discrepancy in study treatment, patients receiving at least one dose of CT-P39 will be treated as “CT-P39” treatment group.

The following analysis sets are Treatment Period II subsets: RAN-TP2, mITT-TP2, PK-TP2, and Safety-TP2 Subsets.

For summaries for Treatment Period II subsets, patients will be analyzed using “CT-P39 300 mg Maintenance”, “Switched to CT-P39 300 mg”, “Xolair 300 mg Maintenance”, “CT-P39 Dose increased”, and “Xolair Dose increased” groups according to the treatment they were initially and subsequently randomized. For PK-TP2 and Safety-TP2 Subsets, patients will be analyzed using one of above five groups, but according to the actual treatment they received in Treatment Period I and II. If there is a patient with such a discrepancy in study treatment, patients receiving at least one dose of CT-P39 will be treated as “CT-P39” treatment group.

The number of patients in all sets and subsets will be tabulated by the treatment group for the RAN Set and its subset for Treatment Period II. A listing will also be produced displaying data on RAN Set.

5.5 Definition of Baseline

The baseline value will be the last non-missing value before the first study drug administration. For the weekly score, the baseline week is comprised of the 7 days prior to Day 1 (Day -7 to -1). Post-baseline values will be all values collected on or after the first study drug administration.

5.6 Protocol Deviations

Protocol deviation will be categorized as "major" or "minor". A major protocol deviation may affect the interpretation of study results or the patient's rights, safety, or welfare, and will be identified during the blinded DRM. Major deviations are defined as follows:

- Significant Good Clinical Practice (GCP) non-compliance (sites which have been closed or patients who have been affected due to scientific misconduct and/or serious GCP non-compliance)
- Mis-randomizations (defined as patients who received a different treatment or different dose to which they were assigned at the randomization)
- Non-adherence to Inclusion and Exclusion criteria which affects efficacy result (to be identified through the review of data sourced from the site monitoring database)
- Receipt of prohibited medication which affects primary efficacy endpoint

Patients who were enrolled in significant GCP non-compliance sites will be excluded from all analysis sets. Patients who were mis-randomized during Treatment Period I will be excluded from PP and PK Sets. Patients who were mis-randomized during Treatment Period II will be excluded only from PK-TP2 Subset for Treatment Period II. Patients with non-adherence to Inclusion and Exclusion criteria which affects efficacy result will be excluded from PP Set. Patients with prohibited medication which affects primary efficacy endpoint will be excluded from PP Set.

The major protocol deviations and other categories used for exclusion will be summarized and listed for all randomly assigned patients including patients from GCP non-compliance sites.

Additionally, protocol deviations due to Coronavirus Disease 2019 (COVID-19) or war in Ukraine with their category and type will be presented in a separate listing for all randomly assigned patients including patients from GCP non-compliance sites.

5.7 Missing Values and Outliers

In general, missing data will not be imputed unless the methods for handling missing data are specified. The handling method of missing values for the primary analysis, comparison of mean change from baseline in ISS7 at Week 12, is presented in Section 9.3.1. Sensitivity analyses are described in Section 9.3.3. Missing daily or weekly ISS, prior and concomitant medications, and adverse events (AEs) will be handled by the methods described in Section 9.2, Section 8.1 and Section 12.1.

Any outliers that are detected during the review of the data will be investigated and discussed during the DRM. In general, outliers will not be excluded but if needed, sensitivity analyses may be conducted excluding outliers to ensure robustness of study conclusions. Details of outliers detected will be presented in the footnotes of the relevant outputs.

6 PATIENT DISPOSITION

The number of patients who were screened and failed at screening will be displayed along with the primary reason for screening failure.

The number and percentage of patients who were randomized, treated with the study drug, discontinued the study drug, terminated from the study in each period, entered Follow-up Period, and completed the study will be displayed for the RAN Set and its subset for Treatment Period II.

The number and percentage of patients who discontinued the study drug will be displayed by primary reason for discontinuation and their time on study treatment prior to discontinuation will be summarized. The treatment duration in days will be calculated as (date of last administration – date of first administration+1). The date of first administration of study drug will be taken as the earliest date recorded on the 'Study Drug Administration' page of eCRF. The date of last dose of study drug will be taken as the last date recorded on the 'Study Drug Administration' page of eCRF.

The number and percentage of patients who terminated the study in each period will also be displayed by primary reason for termination.

Patient disposition will be defined as follows:

- Screened: Patient recorded to agree in 'Informed Consent' page of eCRF and have records in 'Inclusion/Exclusion Criteria' page of eCRF.
- Screening Failure: Patient recorded the screening failure date on 'Inclusion/Exclusion Criteria' page of eCRF.
- Randomized: The randomized ID is recorded on 'Randomization' page of eCRF at Day 1 (Week 0) and at Week 12 for each treatment period.
- Treatment Administered: Study drug administered date is recorded on 'Study Drug Administration' page of eCRF.
- Discontinued Study Treatment: Among patients who were treatment administered, a patient who was not administered study drug at Week 20 on 'Study Drug Administration' page of eCRF or discontinued the study before Week 20.
- Terminated the Study: Patient who answered not to have completed the study on 'End of Study Participation' page of eCRF.
- Entered the Follow-up Period: Patient answered to have entered the Follow-up Period on 'Follow-up Period Yes/No' page of eCRF.

- Completed the Study: Patient who answered to have completed the study on 'End of Study Participation' page of eCRF.

Patient disposition data will be listed for the RAN Set by treatment group. A separate listing of patients reported as screening failures will be provided.

7 DEMOGRAPHICS, BASELINE, AND BACKGROUND CHARACTERISTICS

7.1 Demographics and Stratification Details

The following demographic measures and stratification details recorded on the 'Randomization' page of eCRF will be summarized for the RAN Set and its subset for Treatment Period II: age (years), sex (male, female), fertility status (pre-menarche, surgically sterilized, post-menopausal, potentially able to bear children), weight (kg), height (cm), body mass index (kg/m^2), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, not allowed by investigator country regulations, other) and ethnicity (Hispanic or Latino, non-Hispanic or non-Latino, unknown) as recorded at Screening. Additional baseline information, angioedema presence, will be included in the summary. Patients who answered 'Yes' to the angioedema question in the daily eDiary on any of the days for baseline (Day -7 to -1) will be considered angioedema present at baseline. Patients who answered 'No' to the angioedema question in the daily eDiary on all of the days for baseline (Day -7 to -1) will be considered non-angioedema present at baseline.

The stratification factors for the first randomization, baseline ISS7, weight on Day 1 and country will be summarized. The stratification factors for the second randomization, decrease from baseline in ISS7 at Week 12 and weight at Week 12 will be summarized for the RAN-TP2 Subset. The number and percentage of patients in each stratification level will be presented in the summary; country, baseline ISS7 (< 13 points, ≥ 13 points), weight (< 80 kg, ≥ 80 kg) on Day 1 and Week 12, decrease from baseline in ISS7 at Week 12 (< 5 points, ≥ 5 points).

Demographics and stratification details will be presented in separate listings for the RAN Set by treatment group.

7.2 Viral Serology Test

The following assessments for serologic markers will be performed for baseline eligibility:

- Hepatitis B Surface Antibody (HBsAb)
- Hepatitis B Surface Antigen (HBsAg)
- Hepatitis B Core Antibody (HBcAb)
- Hepatitis C Antibody (HCAb)
- Hepatitis B Virus Deoxyribonucleic Acid (HBV DNA)
- Human Immunodeficiency Virus (HIV) I and II

If the HBsAg test result is positive, the patient will be excluded. If a patient has HBsAg negative and HBcAb positive, a HBV DNA test will be performed at Screening regardless of

HBsAb results. In this case the patient is eligible for this study only when the HBV DNA test result is negative. For patients who were enrolled based on the HBV DNA test, testing of HBsAg, HBsAb, and HBV DNA will be performed at EOT and end-of-study (EOS) visits for monitoring purposes.

HIV test result is negative if screening or confirmation test result is negative. If one of sub type of confirmation test (HIV I or II) is positive, then HIV test will be summarized as positive.

Viral serology will be summarized by treatment group for the RAN Set and RAN-TP2 Subset. All viral serology results including HBV DNA test results will be listed for the RAN Set by treatment group.

7.3 Medical History

Medical history will be captured at Screening and will be coded using Medical Dictionary for Regulatory Activities (MedDRA Version 25.1 or higher). Medical history will be summarized by treatment group, system organ class (SOC) and preferred term (PT) displaying the number and percentage of patients for the RAN Set and RAN-TP2 Subset. The total number of medical history and the number and percentage of patients with at least one medical history will also be presented in the table by treatment group.

Medical history and the CSU diagnosis date will be listed for the RAN Set by treatment group.

7.4 Inclusion and Exclusion Criteria

Details of inclusion and exclusion criteria can be found in sections 4.1.1 and 4.1.2 of the protocol. Non-adherence of inclusion/exclusion criteria patients will be presented in a listing for RAN Set by treatment group.

Inclusion and exclusion criteria may be modified along with protocol revisions. In the case, parameter that indicates under which protocol the patient was recruited and hence which criteria applied for screening will be included in a listing.

7.5 Stool Ova and Parasite Evaluation

Stool ova and parasite examination will be performed on patients with an absolute eosinophil count > 2 × upper limit of normal at Screening and any of risk factors for parasitic disease listed at the exclusion criterion #5.

Stool ova and parasite examination results will be listed for the RAN Set by treatment group.

8 TREATMENTS AND MEDICATIONS

8.1 Prior and Concomitant Medications

All medications taken within 30 days prior to the first study drug administration and until the EOS visit will be collected. The medications will be coded according to the World Health Organization drug dictionary (WHO Drug Dictionary September 2022 or the later version).

Medications will be classified as either prior or concomitant.

For the purpose of inclusion of a medication in prior or concomitant medication tables, incomplete medication start and stop dates will be imputed as follows:

If the stop date is incomplete, the following rules will be applied:

- Missing day: Assume the last day of the month.
- Missing day and month: Assume December 31st.
- Missing day, month and year: Leave it as missing and assume the patient is continuing to take medication.

In the case of the death of a patient, if the imputed stop date is after the date of death, the stop date will be imputed as the date of death.

If the start date is incomplete, the following rules will be applied. If the stop date is incomplete, imputed stop date will be used for the start date imputation:

- Missing day: Assume the first day of the month.

However, if the partial start date and the date of first study drug administration (defined as the earliest date recorded on the 'Study Drug Administration' page of eCRF) lie within the same month and year, and the date of first study drug administration is not after the stop date of the medication, the start date will be set to the date of first study drug administration. If the date of first study drug administration is after the stop date of the medication, then it will be set to stop date of the medication. If the recorded/imputed stop date is missing, the start date will be imputed as the date of the first study drug administration.

- Missing day and month: Assume January 1st.

However, if the partial start date and the date of first study drug administration lie within the same year and the date of first study drug administration is not after the stop date of the medication, the start date will be set to the date of first study drug administration. If the date of first study drug administration is after the stop date of the medication, then it will be set to stop date of the medication. If the recorded/imputed stop date is missing, the start date will be imputed as the date of the first study drug administration.

- Missing day, month and year: Assume date of first study drug administration, if not after the stop date for the medication. Otherwise, the start date will be set to stop date for the medication.

For the missing day imputation, the following examples should be used for reference:

- Example 1:

  Medication start: UNJAN2021

  Medication end: 20MAY2021

  Date of first study drug administration: 16MAY2021

Medication start imputed: 01JAN2021

- Example 2:

  Medication start: UNMAY2021

  Medication end: 20MAY2021

  Date of first study drug administration: 16MAY2021

  Medication start imputed: 16MAY2021

- Example 3:

  Medication start: UNMAY2021

  Medication end: 20MAY2021

  Date of first study drug administration: 24MAY2021

  Medication start imputed: 20MAY2021

A prior medication is defined as any medication that has (recorded or imputed) stop date of medication before the first study drug administration date or answered 'Yes' to whether the medication stops before the first study drug administration on 'Prior & Concomitant Medications' page of eCRF.

The prior medications will be summarized by treatment group, drug class (using Anatomical Therapeutic Chemical [ATC] level 2), and PT along with the total number of prior medications and the number and percentage of patients with at least one prior medication for the Safety Set and its subset for Treatment Period II. When ATC Level 2 for drug class is not available, Level 1 will be used instead.

A concomitant medication is defined as any medication that has (recorded or imputed) stop date which is on or after the date of first study drug administration or still taking the medication ('Ongoing' box checked) on 'Prior & Concomitant Medications' page of eCRF. The concomitant medications will be summarized by treatment period, treatment group, drug class (using ATC level 2), and PT along with the total number of concomitant medications and the number and percentage of patients with at least one concomitant medication for the Safety Set and its subset for Treatment Period II.

Concomitant medications will be summarized for Treatment Period I, Treatment Period II, Follow-up Period, and overall period.

Concomitant medications will be summarized by period as defined follows:

- Treatment Period I: A concomitant medication with a start date prior to the first study drug administration in Treatment Period II, or concomitant medication with a start date prior to (actual or planned) Week 12 visit if a patient discontinues the study drug before

Week 12 but continue the study beyond Week12 or (actual or planned) EOT visit for those patients who have terminated from the study before entering Week 12 visit.

- Treatment Period II: A concomitant medication with a start date between the date of the first study drug administration in Treatment Period II and (actual or planned) EOT visit (both dates inclusive).

- Follow-up Period: For a patient who entered Follow-up Period, a concomitant medication with a start date after (actual or planned) EOT visit.

A concomitant medication for those who have unknown start date and are still taking the medication or have unknown stop date will be included in overall period.

All prior and concomitant medications will be listed separately by treatment group for the Safety Set.

8.2 Nonsedating H_1-Antihistamines

All patients will be allowed to take one predefined nonsedating H_1-antihistamine at an approved dose throughout the study. Patients are permitted to add one additional H_1-antihistamine therapy only during the Follow-up Period or when a patient discontinue the study drug.

The number and percentage of patients who took at least one nonsedating H_1-antihistamine will be tabulated on the Safety Set and its subset for Treatment Period II. In addition, the number and percentage of patients who took each type of H_1-antihistamines will be included in the summary. The same summary for use of additional nonsedating H_1-antihistamine by period will be presented. Additional nonsedating H_1-antihistamine is defined as another medication added, which is different from the currently used nonsedating H_1-antihistamine. Unknown start/stop dates will be imputed and period will be classified in the same way as described in Section 8.1.

A listing will be provided by treatment group for the Safety Set showing the administration details such as drug name, start/stop date, single dose, frequency, and route of administration.

8.3 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 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 number and percentage of patients who were prescribed at least one rescue therapy will be tabulated on the Safety Set and its subset for Treatment Period II. In addition, the number and percentage of patients who took each type of rescue therapy will be included in the summary.

The information of prescribed rescue therapy recorded on the ‘Rescue Therapy’ page of eCRF will be provided by treatment group for the Safety Set. Additional information about daily use of rescue therapy, the number of tablets, will be listed separately as described in Section 9.5.7.

8.4 Exposure to Study Drug

Patients will receive 3 doses of either CT-P39 or Xolair as subcutaneous injections using a PFS every 4 weeks for 12 weeks during each treatment period.

The number and percentage of patients with dose administered will be summarized by treatment group at each scheduled dosing week, along with the number and percentage of patients who did and did not have a complete dose of study drug administered successfully. For patients who were not administered study drug, the number and percentage of patients with each reason why the dose was not administered (Adverse Event, Other) will be displayed by visit. In addition, the frequency of doses received will be summarized by treatment group. All summaries of study drug administration will be based on the Safety Set and its subset for Treatment Period II.

A listing will be provided by treatment group for the Safety Set showing the details of drug administered.

9 EFFICACY ANALYSES

Primary efficacy analyses will be assessed by the change from baseline in ISS7 using two approaches. The first co-primary efficacy evaluation is to compare mean change from baseline in ISS7 of 300 mg of CT-P39 (Arm 1) and 300 mg of Xolair (Arm 2) at Week 12. The other co-primary efficacy evaluation is to assess relative potency of CT-P39 compared to Xolair in terms of change from baseline in ISS7 at Week 12. The primary efficacy analyses will be conducted on the mITT Set and a supportive analysis will be repeated using the PP Set.

All analyses for the secondary efficacy endpoints will be conducted on the mITT and PP Sets and mITT-TP2 Subset at the time points specified in the schedule of events (Appendix 1). All efficacy listings and figures will be based on the mITT Set.

For treatment policy strategy, all available data will be included in the efficacy analysis regardless of adherence to the study drug or use of rescue therapy.

For eDiary data, if the data were recorded repeatedly for the same time point and they have different values, the initial recorded data will be used, unless otherwise specified. eDiary data collected up to EOS date which is recorded on the eCRF will be used for the calculation of efficacy endpoints.

9.1 Determination of Study Week

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

Table 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 the week prior to a study treatment visit except for Week 1. For example, 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.

- **Weeks prior to a study treatment visit (Weeks 4, 8, 12, 16, and 20):** The time period of the study week starts from the first study day of that week (Table 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 (Weeks 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 1). If the last study day of the week is earlier than the study treatment visit then the week and its weekly score will not be presented.

Examples of patient visits and the study days used to calculate the weekly scores are shown in Table 2.

Table 2 Examples of Study Week Determination

	Protocol-defined	Example 1	Example 2	Example 3	Example 4
Week 4 visit	Day 29	Day 27	Day 32	Day 33	Day 38
Time period for Week 4	Day 22 – 28	Day 22 – 26	Day 22 – 28	Day 22 – 28	Day 22 – 28
Time period for Week 5	Day 29 – 35	Day 29 – 35	Day 32 – 35	Day 33 – 35	Missing
Time period for Week 6	Day 36 – 42	Day 36 – 42	Day 36 – 42	Day 36 – 42	Day 38 – 42

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 9.2.

Study week will be calculated as described above, but if the study week contains days which must be followed treatment visit but are earlier of actual treatment visit, only portion of study

days which comes later of actual treatment visit will be used for calculating the corresponding weekly score.

9.2 Calculation of Weekly Scores

The weekly score (ISS7, weekly hives severity score [HSS7] and weekly urticaria activity score [UAS7]) 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. eDiary entries on or after 24:00 and prior to 6:00 am are considered as evening scores for the previous days. 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 9.1, 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, and then multiplied by 7.

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

Examples of calculating weekly scores are shown in Table 3.

Table 3 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							

9.3 Co-Primary Efficacy Evaluations

The primary endpoint is the change from baseline in ISS7 at Week 12 which is defined as ISS7 at Week 12 minus the baseline ISS7. The ISS7 is the sum of the daily ISS over 7 days and ranges from 0 to 21. The daily ISS is the average of the morning and evening scores on a scale of 0 (none) to 3 (severe). The baseline ISS7 is the sum of the daily ISS over the 7 days (Day -7 to -1) prior to the first study drug administration.

There will be co-primary evaluations for the primary endpoint to evaluate therapeutic equivalence between CT-P39 and Xolair.

9.3.1 Comparison of Mean Change from Baseline in ISS7 at Week 12

One of the primary efficacy evaluations is to compare mean change from baseline in ISS7 of 300 mg of CT-P39 (Arm 1) and 300 mg of Xolair (Arm 2) at Week 12, calculated as ISS7 at

Week 12 minus the baseline ISS7. The analysis will be conducted by analysis of covariance (ANCOVA) coupled with Multiple imputation (MI) with the Missing at random (MAR) assumption. The ANCOVA model will include the treatment group as a fixed effect and baseline ISS7, body weight on Day 1 and country as covariates. Countries can be pooled into a region (EMEA [Bulgaria, Greece, Hungary, Poland, Ukraine] versus Asia [Korea]) for statistical models when there are not sufficient patients within each country.

MI with the MAR assumption will be applied using MI procedure in SAS®. All patients with baseline ISS7 in mITT Set will be included in the analysis. The multiple imputed datasets will be generated based on linear regression models on change from baseline in 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. Ten imputed datasets will be generated. If the imputed value of change from baseline in ISS7 at Week 12 is not plausible, that is, the value of ISS7 at Week 12 calculated from imputed value is not bounded by (0, 21), ISS7 at Week 12 will be replaced with 0 or 21 when the calculated ISS7 at Week 12 is under 0 or over 21 respectively. After replacement, the change from baseline value will be adjusted using this replacement (adjusted change from baseline in ISS7 at Week 12 = [replaced] ISS7 at Week 12 - ISS7 at baseline) and replace the originally imputed value. ANCOVA for the mean change from baseline in ISS7 at Week 12 will be applied to each of the imputed datasets to gain estimates for the least squares means and their standard errors. The ANCOVA results from each set of imputed datasets will then be pooled using MIANALYZE procedure in SAS® based on Rubin's rule for final statistical inference. For the demonstration of efficacy, point estimate and 90% CI for the difference in the mean change from baseline in ISS7 at Week 12 between CT-P39 (300 mg) and Xolair (300 mg) will be computed. Therapeutic equivalence will be concluded if the 90% CI for the treatment difference is entirely within an equivalence margin [-2.5, 2.0].

9.3.2 Relative Potency

The other primary efficacy evaluation is to assess the relative potency. The relative potency of CT-P39 to Xolair is defined as the ratio of equally effective dose of CT-P39 relative to that of Xolair. The therapeutic response will be estimated by the change from baseline in ISS7 at Week 12. Since the two treatments will be compared at the same two-dose levels (300 mg and 150 mg), a 4-point assay will be used to calculate the relative potency and its CI.

Log dose-therapeutic response curves for each treatment group will be estimated by linear regression. The change from baseline in ISS7 at Week 12 and dose in the log scale will be considered as a response variable and independent variable respectively. The baseline ISS7, body weight and country will be included in a model as covariates. The log relative potency will be estimated as the ratio between the estimate of the overall product effect and the estimate of the common slope of log dose. The overall product effect is defined as the difference in response between treatment groups (y-intercepts difference). The calculation of the CI of log relative potency will be based on Fieller's theorem (Fieller, 1940, 1954). The estimate for log relative potency and its CI will be exponentiated. Countries can be pooled into a region (EMEA [Bulgaria, Greece, Hungary, Poland, Ukraine] versus Asia [Korea]) for statistical models when there are not sufficient patients within each country.

The estimate of overall treatment effect, common slope of log dose, relative potency and its corresponding CI will be presented. Statistical equivalence will be declared if the two-sided

90% CI for the relative potency falls entirely within a predefined margin of [0.5, 2.0].

9.3.3 Sensitivity Analysis

To assess the robustness of analysis result, a tipping point approach for comparison of mean change from baseline in ISS7 at Week 12 will be applied, where by the impact of missing data on the conclusions will be assessed. The tipping points are defined to be the particular setting for the missing values that would change the study's conclusions. MI under the Missing Not at Random (MNAR) assumption will be applied to search for a tipping point by using "shift" approaches until the conclusion is reversed. Imputed values will be shifted gradually by treatment groups (CT-P39 300 mg vs. Xolair 300 mg) to make MNAR scenarios. A point estimate and 90% CI for treatment difference will be provided using the same analysis method for the primary analysis as specified in Section 9.3. The setting where CI no longer rules out differences in the primary endpoint for the therapeutic equivalence margin of [-2.5, 2.0] will be displayed.

9.4 Analysis of Secondary Efficacy Endpoints

9.4.1 Weekly Itch Severity Score (ISS7)

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 at each week up to Week 40 will be summarized by treatment group. Change from baseline in ISS7 at every week up to Week 40 will be graphically presented for the mITT Set.

The ISS7 at each week will be listed by treatment group.

9.4.2 Minimally Important Difference (MID) in Weekly Itch Severity Score

The MID response in ISS7 is defined as a reduction of 5 points or more from baseline for ISS7.

For MID response assessment, following summaries will be reported:

- Time to the MID response by Week 12
- Percentage of MID responder in the ISS7 at Weeks 8, 12 and 24

The number and percentage of patients who achieved MID response up to Week 12 and patients classified as non-responders with corresponding reason will be presented.

Time to MID response is the time (in weeks) from Day 1 to the study week when MID response is first achieved up to Week 12; the study week for which the change from baseline in ISS7 is $\leq$ -5. If a patient fails to achieve an MID response up to Week 12 or terminates the study prior to Week 12 without achieving MID response, it will be censored at the date of the last non-missing ISS7 evaluation. The 25th percentile, median, 75th percentile with corresponding 95% CI, minimum and maximum of the time to achieve first MID response will also be summarized for each treatment group. Statistics will be estimated using the Kaplan-Meier method. Kaplan-

Meier estimates of the distribution of time to first MID response will be presented graphically.

The number and percentage of patients who achieved MID response at Week 8, Week 12 and Week 24 will be summarized by each treatment group. If a patient has missing weekly scores for the given week the patient will be classified as a non-responder.

Time to MID response by Week 12, whether a patient is censored and censored time will be provided within the ISS7 listing.

9.4.3 Weekly Hives Severity Score (HSS7)

The HSS7 is the sum of the daily HSS over 7 days and ranges from 0 to 21. The HSS will be measured twice daily (morning and evening) and determined based on the number of hives (wheals) such as score of 0 (none), 1 (between 1 and 6 hives/12 hour), 2 (between 7 and 12 hives/12 hour), and 3 (> 12 hives/12 hour). The daily HSS is the average of the morning and evening scores. The baseline score is the sum of the daily HSS over the 7 days (Day -7 to -1) prior to the first study drug administration.

Descriptive statistics for actual value and change from baseline at each week up to Week 40 will be summarized by treatment group. Change from baseline in HSS7 at every week up to Week 40 will be graphically presented for the mITT Set.

The HSS7 at each week will be listed by treatment group.

9.4.4 Weekly Urticaria Activity Score (UAS7)

The UAS7 is the sum of the daily UAS over 7 days and ranges from 0 to 42. The daily UAS (range 0-6) will be calculated as the average of the sum of morning and evening scores of the two components: (1) ISS (range 0-3) and (2) HSS (range 0-3). The baseline UAS7 is the sum of the daily UAS over the 7 days (Day -7 to -1) prior to the first study drug administration.

The following UAS7 summaries will be reported:

- Change from baseline in UAS7 at Weeks 8, 12, and 24
- Patients with UAS7 of ≤ 6 at Weeks 8, 12, and 24
- Percentage of complete responders (UAS7 = 0) at Weeks 8, 12 and 24

Descriptive statistics for actual value and change from baseline at each week up to Week 40 will be summarized by treatment group. Change from baseline in UAS7 at every week up to Week 40 will be graphically presented for the mITT Set.

The number and percentage of patients whose UAS7 is in each response category will be summarized by treatment group. If a patient has missing weekly scores for the given week the patient will be classified as a non-responder.

The UAS7 at each week will be listed by treatment group.

9.4.5 Angioedema-Free Days

The proportion of angioedema-free days from Week 4 to Week 12 is 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 Week 4 visit date and ending the day prior to Week 12 visit date. If Week 4 or Week 12 visit date is missing, planned visit date is used. Patients who have missing responses for > 40% of the daily diary entries between Week 4 visit date and Week 12 visit date 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 Week 4 to Week 12 will be presented by each treatment group.

A listing will be provided by treatment group, showing response to the angioedema question and follow-up action if there is a reported angioedema.

9.4.6 Comparison of Rescue Therapy Use

The number of tablets for each 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. When one or more of the daily records are missing, the same principles described in Section 9.2 will be applied for calculation of the number of weekly tablets. 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. If the medication or its dose which is not pre-defined in protocol was taken, the maximum permitted number will be standardized on a case-by-case manner at the blinded DRM.

Descriptive statistics for actual value and change from baseline in number of tablets per week of rescue therapy at Weeks 8, 12, 24, and 40 will be summarized by each treatment group. If a subject switches rescue therapy medication and starts a different medication or the prescribed dose of the rescue therapy medication is changed during the study, the subject will be excluded from the summary.

The number of tablets per week of rescue therapy for each patient will be listed by treatment group.

10 QUALITY OF LIFE ANALYSES

QoL will be assessed using the validated DLQI and CU-Q_2oL at the time points specified in the schedule of events (Appendix 1). QoL data which has the same visit date with the corresponding visit date in eCRF will be used and analyzed under the visit name recorded in eCRF. If there are duplicated data with the same date but different values, the initial recorded data will be used.

All analyses for QoL endpoints will be conducted on the mITT and PP Sets and mITT-TP2 Subset at the time points specified in the schedule of events (Appendix 1). Listings will be based on the mITT Set.

10.1 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 (not at all) to 3 (very much). The overall DLQI score is the sum of the individual domain scores and ranges from 0 to 30.

Overall DLQI scores will be summarized using descriptive statistics of actual value and change from baseline at scheduled visits.

Scores for individual 10 items and overall score will be listed by treatment group and time point.

10.2 Chronic Urticaria Quality of Life Questionnaire

The CU-Q_2oL is a 23-item CSU-specific health-related QoL questionnaire across 6 domains: pruritus, swelling, impact on life activities, sleep problems, limits, and looks (Baiardini *et al.,* 2005). 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). The overall raw score is sum of individual raw domain scores and ranges from 23 to 115.

Overall raw scores of CU-Q_2oL will be converted to 0 to 100 point scores according to the following formula:

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

In the formula, minimum value is 23 (1 score for all 23 item) and maximum value is 115 (5 score for all 23 items). Converted overall CU-Q_2oL scores will be summarized using descriptive statistics of actual value and change from baseline at scheduled visits.

Scores for individual 23 items and overall raw and converted scores will be listed by treatment group and time point.

11 PHARMACOKINETIC ANALYSES

Blood samples for PK analyses will be collected at time points specified in the schedule of events (Appendix 1). All concentration below lower limit of quantification (BLQ) values will be treated as zero (0) for PK parameter summary.

Serum concentrations of omalizumab at each scheduled visit will be presented in the listing for the Safety Set.

The secondary PK endpoint is trough serum concentration (C_{trough}) of omalizumab. The C_{trough} is observed concentration prior to the next scheduled visit. Descriptive statistics (n, mean, SD, geometric mean, CV%, minimum, median, and maximum) for C_{trough} at each dose will be presented by treatment group at each scheduled visit (Appendix 1) on the PK Set and its subset for Treatment Period II.

C_{trough} at each scheduled visit will be presented in the listing for the PK Set.

12 SAFETY ANALYSES

All safety analyses will be performed in the Safety Set and its subset for Treatment Period II by treatment group.

All safety data will be listed and summarized for the Safety Set, unless otherwise specified. The safety endpoints will be evaluated under a treatment policy strategy regardless of adherence to the study drug or use of rescue therapy.

12.1 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. All AEs will be documented in the eCRF by the Investigator regardless of their relationship to study drug or their clinical significance from the time of signing the informed consent form (ICF). AEs assessed from the date the ICF is signed until up to EOS visit will be collected.

The MedDRA version 25.1 or higher will be used to code all AEs. AEs will be graded for intensity according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to exposure to study drug or any event already present that worsens in either severity or frequency after exposure to study drug.

For the purpose of inclusion in TEAE tables, incomplete AE start and stop dates will be imputed as follows:

If the stop date of an AE is partial or missing the following rules will be applied.

- Missing day: Assume the last day of the month.
- Missing day and month: Assume December 31st.
- Missing day, month and year: Leave it as Missing.

In the case of the death of a patient, if the imputed stop date is after the date of death the stop date will be imputed as the date of death.

If the start date of an AE is partial or missing, the following rules will be applied. If the stop date of the AE is partial, imputed stop date will be used instead.

- If the day of an AE is missing, the month and year of the partial date will be compared to the date of the first exposure to study drug.
  - If the month and year are equal for both dates, the AE start date will be imputed as the earlier date of: (i) the date of the first exposure to study drug, and (ii) the stop date of the AE. If the AE stop date is missing, the AE start date will be imputed as the date of the first exposure to study drug.
  - If the month or year are not equal, the AE start date will be imputed as the first day of the month.

- If the day and month are missing, the year of the partial date will be compared to the date of the first exposure to study drug.
  - If the years of both dates are equal, start date will be imputed as the earlier date of: (i) the date of the first exposure to study drug, and (ii) the stop date of the AE. If the AE stop date is missing, the AE start date will be imputed as the date of the first exposure to study drug.
  - If the years are not equal, start date will be imputed as the 1st of January of the years of the partial date.
- If the AE start date is missing, start date will be imputed as the earlier date of: (i) the date of the first exposure to study drug, and (ii) the stop date of the AE. If the AE stop date is missing, the AE start date will be imputed as the date of the first exposure to study drug.

The recorded/imputed dates of AEs will be used for the decision of whether the event is TEAE and in classification of treatment periods.

TEAEs will be summarized for Treatment Period I, Treatment Period II, Follow-up Period, and overall period.

TEAEs will be summarized by period as defined follows:

- Treatment Period I: A TEAE with a start date prior to the first study drug administration in Treatment Period II, or TEAE with a start date prior to (actual or planned) Week 12 visit if a patient discontinues the study drug before Week 12 but continue the study beyond Week12 or (actual or planned) EOT visit for those patients who have terminated from the study before entering Week 12 visit.

- Treatment Period II: A TEAE with a start date between the date of the first study drug administration in Treatment Period II and (actual or planned) EOT visit (both dates inclusive).

- Follow-up Period: For a patient who entered Follow-up Period, a TEAE with a start date after (actual or planned) EOT visit.

Listings for AEs will include the following information: SOC, PT and Verbatim term; start and stop date/time; TEAE flag, treatment period (Treatment Period I, Treatment Period II, Follow-up Period), Serious Adverse Event (SAE) flag, outcome (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown), any treatment received (no, medication, non-medication treatment, both medication and non-medication treatment), intensity (CTCAE Grade 1 to 5), action taken with study drug (dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable), relationship with study drug (unrelated, possible, probable, definite), adverse event of special interest (AESI) flag.

In summaries, AEs will be considered to be related if the relationship is possible, probable, or definite. If relationship or intensity is missing, it will be summarized separately under a missing category.

12.1.1 Treatment-Emergent Adverse Events

The TEAEs during the study will be summarized by treatment group and SOC, PT, relationship and intensity, displaying the number and percentage of patients with at least one TEAE using only the worst intensity recorded at each level of summarization. The total number of events and number of patients with at least one TEAE over all SOCs will also be displayed.

12.1.2 Serious Adverse Events

A SAE is defined as any event that is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or results in death. Important medical events that may not result in death, be life threatening, or require hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in the definition may be considered a SAE when, based upon appropriate medical judgment.

Treatment-Emergent Serious Adverse Events (TESAEs) will be summarized by treatment group and SOC, PT, relationship and intensity, displaying the number and percentage of patients with at least one TESAE using only the most severe TESAE recorded at each level of summarization. The total number of events and number of patients with at least one TESAE over all SOCs will also be displayed.

All SAEs will be listed including a subset of the variables detailed in Section 12.1. Serious criteria with additional SAE description will be presented in an additional information listing.

12.1.3 Deaths

All patients who have a SAE with serious criteria of “Death” will be presented in a listing and the following variables will be included; date of first/last dose, date of last visit, date of death, days on study, TEAE flag, SOC, PT, cause of death, autopsy after death (yes, no), completion of death certificate (yes, no) and relationship to study drug. In case of death during the study, days on study will be calculated as (date of death – date of first dose + 1). Otherwise, days on study will be calculated as (date of last visit – date of first dose + 1).

12.1.4 Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation

All patients who have a TEAE with an action taken with study drug of “Drug Withdrawn” will be summarized by treatment group and by SOC, PT, relationship and intensity, displaying the number and percentage of patients with at least one TEAE leading to study drug discontinuation, using only the most severe TEAE recorded at each level of summarization. The total number of events and number of patients with at least one TEAE which led to study drug discontinuation will also be displayed.

All TEAEs leading to study drug discontinuation will be listed including a subset of the variables detailed in Section 12.1.

12.1.5 Treatment-Emergent Adverse Events of Special Interest

The TEAEs of special interest will be defined as following:

- Allergic reaction type I/anaphylaxis: TEAEs and patient answered "Yes" to the question on Allergic reaction Type I/Anaphylaxis and recorded as allergic reaction type I or anaphylaxis on "Adverse Event" page of eCRF

- Injection site reactions (ISR): TEAEs and patient answered "Yes" to the question on Injection Site Reaction on "Adverse Event" page of eCRF

- Allergic reaction type III (Serum sickness/serum sickness-like reaction): TEAEs and patient answered "Yes" to the question on Allergic reaction type III (Serum sickness/Serum sickness-like reaction) and recorded as allergic reaction type III on "Adverse Event" page of eCRF

- Parasitic (helminth) infections: TEAEs and High-Level Group Terms is 'Helminthic disorders'.

TEAEs of each special interest will be summarized in separate tables. These are displayed by treatment group, SOC, PT, relationship and intensity, displaying the number and percentage of patients with at least one TEAE using only the most severe TEAE recorded at each level of summarization.

TEAEs classified as allergic reaction type I/anaphylaxis, ISR, and allergic reaction type III (serum sickness/serum sickness-like reaction) will be presented in separate listings including a subset of the variables detailed in Section 12.1. Additional information about experienced signs and symptoms for TEAEs classified as special interest will be presented in separate tables and listings.

12.2 Clinical Laboratory Evaluations

Blood and urine samples for clinical laboratory assessments will be collected at the time points specified in the schedule of events (Appendix 1).

For laboratory parameters with numeric results, actual values and changes from baseline will be summarized using descriptive statistics by treatment group, laboratory category, test parameter and visit. All numeric values recorded BLQ or above the upper limit of quantification are set to their respective limits for all summaries.

Laboratory parameters with categorized results will be labeled with "Normal" or "Abnormal" and then summarized in a shift table from baseline by each scheduled visit. The number and percentage of patients will be displayed for post-baseline visits by treatment group, laboratory category, test parameter and visit.

Laboratory numeric parameters will be labeled with a CTCAE term and CTCAE grading will be applied to post-baseline values where possible according to CTCAE version 5.0. Grades that require clinical input only will not be assigned to these parameters. Grades which are part numeric and part clinical input will be assigned based on the numeric portion only. If different grades share the same criteria due to exclusion of clinical input, a lower grade will be used.

The CTCAE terms and ranges for applicable parameters are listed in Appendix 2. The CTCAE grades will be Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe) and Grade 4 (Life-threatening). The CTCAE Grade 5 (Death) will not be applied in this analysis since death cannot be determined from a numeric laboratory result. If the post-baseline result for a patient does not satisfy any CTCAE grade, it will be classified as "No Grade".

The number and percentage of patients by laboratory category, treatment group and CTCAE term will be summarized using the most severe grade after the first study drug administration for each treatment period. The period will be classified in the same way as described in Section 8.1 and Section 12.1. The most severe grade will be selected including all post-baseline scheduled and unscheduled visits in each period.

All clinical laboratory results of clinical chemistry, hematology and urinalysis will be presented in separate listings along with high and low flags, if applicable, to show if a value was outside the normal range and CTCAE results for applicable parameters. The summaries and listings will be based on the system international (SI) units.

Results from central laboratory will be included in summaries and listings will contain all results from laboratories.

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, creatine kinase-myocardial band isoenzyme
Hematology:	Hemoglobin, hematocrit, red blood cell count, total and differential white blood cell count, absolute lymphocyte count, absolute neutrophil count, absolute eosinophil count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count
Urinalysis:	Color, pH, specific gravity, glucose, ketones, nitrite, protein, bilirubin, urobilinogen, blood, leucocyte, microscopic examination [1]

[1] Microscopic examination results will be presented in the listing only.

12.3 Total and Free Serum Immunoglobulin E (IgE)

Blood samples for total and free serum IgE will be obtained at the time points specified in the schedule of assessments (Appendix 1). Total and free IgE samples will be analyzed at the central laboratory.

Total IgE concentrations that are BLQ (< 2 IU/mL) will be set to zero for summary table. Free IgE concentrations that are BLQ (< 6.25 ng/mL) will be set to lower limit of quantification (LLoQ) (6.25 ng/mL) and above upper limit of quantification (ULoQ) values (> 400 ng/mL) will be set to ULoQ (400 ng/mL). For total IgE, if the data were recorded repeatedly for the same time point and they have different values, the largest value will be used for the summary as determined in the blinded DRM.

Summary table presenting descriptive statistics (n, mean, SD, geometric mean, CV%, minimum, median, and maximum) for serum concentrations of total and free serum IgE will be presented by treatment group at each scheduled visit. Serum concentration data will be also listed by patient at each visit with sampling date/time. Total and free IgE level will be presented in the unit, IU/mL.

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

Complement (C3, C4) and total hemolytic complement (CH_{50}) will be assessed at Day 1 prior to the study drug administration to establish the baseline value. Additional serum samples for complement (C3, C4) and total hemolytic complement (CH_{50}) to determine serum sickness will be assessed if allergic reaction type III, including serum sickness/serum sickness-like reaction, is suspected at Investigator's discretion. All complement tests data will be presented in a listing by treatment group.

12.5 Vital Signs and Weight

Vital signs (including systolic and diastolic blood pressure [BP], heart rate, respiratory rate and body temperature) and weight will be assessed at scheduled visits prior to beginning of the study drug administration. For hypersensitivity/allergic reactions monitoring, vital signs will also be assessed at the following time points of scheduled visit:

- Prior to the study drug administration (within 30 minutes)
- 1 hour (±10 minutes) after the end of the study drug administration

In addition, hypersensitivity/allergic reactions will be monitored by routine continuous clinical monitoring, including patient-reported signs and symptoms. All vital signs data and weight will be summarized using descriptive statistics of actual value and change from baseline by treatment group and parameter at each scheduled visit. The number and percentage of patients with a clinically notable vital sign result (Low or High) will be summarized by treatment group, visit, time point and parameter in the table. The criteria for clinically notable results are defined as follows:

Parameter	Low	High
Systolic blood pressure (mmHg)	≤ 90	≥ 160
Diastolic blood pressure (mmHg)	≤ 50	≥ 90
Heart rate (beats per minute)	≤ 50	≥ 100
Respiratory rate (breaths per minute)	≤ 12	≥ 20
Body temperature (^{o}C)	≤ 35.0	≥ 38.0

In addition, all results of vital signs including hypersensitivity monitoring results and weight will be listed by treatment group, visit, time points and parameter. High and low flags will also be presented in the listing to show whether a value is outside of the normal range.

12.6 Electrocardiograms

12-lead electrocardiograms (ECGs) will be performed at the time points specified in the schedule of events (Appendix 1) and additional ECG can be performed if the patient experienced cardiac symptoms during study drug administration. Findings of 12-lead ECG will be classified as either ("Normal", "Abnormal, Not Clinically Significant", or "Abnormal, Clinically Significant").

The number and percentage of patients will be summarized by treatment group and visit, in the form of a shift table to detect changes from baseline. All 12-lead ECGs data will be listed by treatment group and visit. In addition, all ECG data for hypersensitivity reactions monitoring will be listed within ECG listing.

12.7 Physical Examination

Physical examinations will be performed before study drug administration at the time points specified in the schedule of events (Appendix 1). Findings of physical examination will be collected as either ("Normal", "Abnormal, Not Clinically Significant", or "Abnormal, Clinically Significant").

The number and percentage of patients will be summarized in a table by treatment group, visit and body system, in the form of a shift table to detect changes from baseline. All physical examination data will be listed for each patient by treatment group, visit and body system.

12.8 Pregnancy Test

Pregnancy tests will be conducted and summarized only for female patients of childbearing potential. Pregnancy tests consist of serum and urine pregnancy tests. Serum pregnancy tests will be performed for women of childbearing potential who have not been surgically sterilized at Screening and EOS visit. Serum pregnancy test results will be classified as either ("Positive", "Negative" or "Indeterminate"). Only patients with a negative serum pregnancy test results can be enrolled in the study.

Urine pregnancy tests 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). Urine pregnancy

test results will be classified as either ("Positive", "Negative", or "Equivocal"). If a urine pregnancy test result is "Positive" or "Equivocal", a confirmatory serum pregnancy test should be performed.

The number and percentage of the results of serum and urine pregnancy test will be summarized by treatment group and visit. All pregnancy test results will be listed for each patient tested by treatment group and visit.

12.9 Immunogenicity

Serum samples for immunogenicity testing will be collected prior to dosing of study drug at the time points specified in the schedule of events (Appendix 1), EOT and EOS. Additional serum samples for immunogenicity testing may be collected if a patient experiences immune-related AEs. Immunogenicity will be assessed by anti-drug antibody (ADA) and neutralizing antibody (NAb).

The ADA assay will follow a three-tiered approach consisting of (i) screening assay, (ii) confirmatory assay, and (iii) titration. The test outcome for the screening assay will be reported as 'Positive' or 'Negative'. Samples that are 'Positive' in the screening assay will be undergone further testing in the confirmatory assay to determine if samples are a true positive. The test outcome for the confirmatory assay will be 'Positive', 'Negative', and 'Not applicable (N/A)'. 'Positive' indicates a true positive test outcome and will be labeled as 'Positive' in outputs. 'Negative' is considered negative, and 'N/A' indicates the assay was negative at the screening phase of the process. Samples with a 'Negative' test outcome for either screening or confirmatory assays will be considered negative for the overall ADA assessment. For further characterization, the antibody level will be assessed by titration in confirmed positive samples. Samples that are positive in the ADA confirmatory assay will be analyzed further to conduct a NAb assessment. The test outcome for the screening assay will be: ("Positive" or "Negative").

The results of the final ADA assay and the final NAb assay will be summarized. The number and percentage of patients will be provided by treatment group and visit. A listing showing immunogenicity test results from each three-tiered approach for each patient will be provided by treatment group and visit.

13 CHANGES FROM PROTOCOL

- Section 7.4.3.1 and 7.4.3.2 of the protocol (version 2.3 A.0) states that individual domain scores and overall scores of DLQI and CU-Q_2oL will be summarized. Since individual scores have a significant clinical meaning when they are integrated into the overall scale, only overall scores will be summarized.

- Section 7.4.4 of the protocol (version 2.3 A.0) states that serum concentrations of omalizumab and C_{trough} will be summarized. Since each PK blood sampling is scheduled right before the study drug administration, C_{trough} would be the same as the concentration right before the study drug administration. Therefore, the serum concentration will be summarized as C_{trough}.

- Section 7.4.5 of the protocol (version 2.3 A.0) states that incidence rate of AESI and its difference between treatment arms will be presented with their 95% CI. Since the

number of AESI is not expected to be high enough to compare statistically using the difference estimate and its CI, only the total number of AESI and patient number with AESI will be summarized.

14 REFERENCE LIST

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15 APPENDIX

Appendix 1: Schedule of Events

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 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 of the protocol [CT-P39 3.1]).
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: Table of CTCAE Terms and Grades

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Alanine aminotransferase increased	Alanine Aminotransferase (ALT)	High	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alkaline phosphatase increased	Alkaline phosphatase (ALP)	High	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Anemia	Hemoglobin	Low	<LLN - 10.0 g/dL; <LLN – 6.2 mmol/L; <LLN - 100 g/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 – 80 g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L	-
Aspartate aminotransferase increased	Aspartate Aminotransferase (AST)	High	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Blood bilirubin increased	Total Bilirubin	High	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Cholesterol high	Total Cholesterol	High	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
CPK increased	Creatine Phosphokinase (CPK)	High	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
Creatinine increased [1)]	Creatinine	High	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN

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GGT increased	Gamma Glutamyl Transferase (GGT)	High	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Hemoglobin increased	Hemoglobin	High	Increase in >0 - 2 g/dL from ULN	Increase in >2 - 4 g/dL from ULN	Increase in >4 g/dL from ULN	-
Hyperkalemia	Potassium	High	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Hypermagnesemia	Magnesium	High	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L;
Hypernatremia	Sodium	High	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L;	>160 mmol/L
Hypertriglyceridemia	Triglyceride	High	150 - 300 mg/dL; 1.71 - 3.42 mmol/L	>300 - 500 mg/dL; >3.42 - 5.7 mmol/L	>500 - 1000 mg/dL; >5.7 - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L
Hypoalbuminemia	Albumin	Low	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL;<20 g/L	-
Hypoglycemia	Glucose	Low	<LLN-55mg/dL; <LLN-3.0 mmol / L	< 55 -40mg/dL; < 3.0 – 2.2 mmol / L	< 40 -30mg/dL; < -2.2 – 1.7 mmol / L	<30mg/dL; <1.7mmol/L
Hypokalemia	Potassium	Low	<LLN - 3.0 mmol/L	-	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Hypomagnesemia	Magnesium	Low	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L;
Hyponatremia	Sodium	Low	<LLN - 130 mmol/L	125-129 mmol/L	120-124 mmol/L regardless of symptoms	<120 mmol/L
Leukocytosis	White Blood Cells	High	-	-	>100,000/mm^3	-
Neutrophil count decreased	white blood cell count with differential count	Low	<LLN - 1500/mm^3; <LLN - 1.5 x $10e^9$ /L	<1500 - 1000/mm^3; <1.5 - 1.0 x $10e^9$ /L	<1000 - 500/mm^3; <1.0 - 0.5 x $10e^9$ /L	<500/mm^3; <0.5 x $10e^9$/L
Platelet count decreased	Platelet count	Low	<LLN - 75,000/mm^3; <LLN - 75.0 x $10e^9$ /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x $10e^9$ /L	<50,000 - 25,000/mm^3; <50.0 - 25.0 x $10e^9$ /L	<25,000/mm^3; <25.0 x $10e^9$ /L

LLN = lower limit of normal, ULN = upper limit of normal.
1) The most severe grade is counted if the CTCAE grade is discrepant by multiple definitions.

Note: The LLN and ULN values will be the lower and upper limits of the normal ranges as provided by the central laboratory at each relevant transfer. In case numeric value for grading is identical such as Hypokalemia, CTCAE grade which includes numeric value will only be applied, because abnormal laboratory value with clinical input was reported as an adverse event and graded accordingly.