CLINICAL STUDY PROTOCOL

A Phase 1, Randomized, Double-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics and Safety of Three Formulations of Omalizumab (CT-P39, EU-approved Xolair, and US-licensed Xolair) in Healthy Subjects

Protocol Number CT-P39 1.1

Sponsor: CELLTRION, Inc.

[redacted]

Sponsor Contact:

[redacted]

SAE Reporting and Data Center:

[redacted]

Version and Date of Protocol: Protocol Version 2.0, 20 April 2020

CONFIDENTIAL

Protocol Approval

Study Title:	A Phase 1, Randomized, Double-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics and Safety of Three Formulations of Omalizumab (CT-P39, EU-approved Xolair, and US-licensed Xolair) in Healthy Subjects
Protocol Number:	CT-P39 1.1
Protocol Date:	Protocol Version 2.0, 20 April 2020

Protocol accepted and approved by:

[redacted]

Signature

Date

Declaration of Investigator

[redacted]

I have read and understood all sections of the protocol entitled "A Phase 1, Randomized, Double-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics and Safety of Three Formulations of Omalizumab (CT-P39, EU-approved Xolair, and US-licensed Xolair) in Healthy Subjects" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Version 2.0, dated 20 April 2020, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use harmonised tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with CELLTRION, Inc. or implement protocol changes without institutional review board approval except to eliminate an immediate risk to subjects. I agree to administer study drug only to subjects under my personal supervision or the supervision of a sub-investigator.

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

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

Signature of Principal Investigator

Date

Printed Name of Principal Investigator

Declaration of Investigator

[redacted]

I have read and understood all sections of the protocol entitled "A Phase 1, Randomized, Double-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics and Safety of Three Formulations of Omalizumab (CT-P39, EU-approved Xolair, and US-licensed Xolair) in Healthy Subjects" and the accompanying investigator's brochure.

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Signature of Principal Investigator	Date

Printed Name of Principal Investigator

PROTOCOL SYNOPSIS

Title: A Phase 1, Randomized, Double-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics and Safety of Three Formulations of Omalizumab (CT-P39, EU-approved Xolair, and US-licensed Xolair) in Healthy Subjects

Protocol Number: CT-P39 1.1

Development Phase: Phase 1

Sponsor: CELLTRION, Inc.

Principal Investigators: [redacted]

Study Center(s): 2 sites; [redacted]

Study Objective(s):

This study consists of 2 parts with separate purposes. The objective of Part 1 is to evaluate the initial safety of CT-P39, compared to that of European Union (EU)-approved Xolair and the objective of Part 2 is to demonstrate similarity in pharmacokinetics (PK) of CT-P39, EU-approved Xolair and United States (US)-licensed Xolair.

Primary objective (*Part 2*)

- To demonstrate PK similarity in terms of area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$), area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-}last}$), and maximum serum concentration (C_{max}) of CT-P39, EU-approved Xolair, and US-licensed Xolair in healthy subjects (CT-P39 to EU-approved Xolair, CT-P39 to US-licensed Xolair, and EU-approved Xolair to US-licensed Xolair)

Secondary objectives

Data for each part will be independently analyzed and presented.

Part 1

- To evaluate initial safety up to Day 29 in terms of treatment-emergent adverse events of CT-P39, compared to that of EU-approved Xolair in healthy subjects
- To assess additional safety, PK, pharmacodynamics (PD), and immunogenicity of CT-P39 and EU-approved Xolair in healthy subjects up to Day 29

Both parts

- To assess additional safety, PK, PD, and immunogenicity of CT-P39, EU-approved Xolair, and US-licensed Xolair in healthy subjects up to Day 127

Study Design:

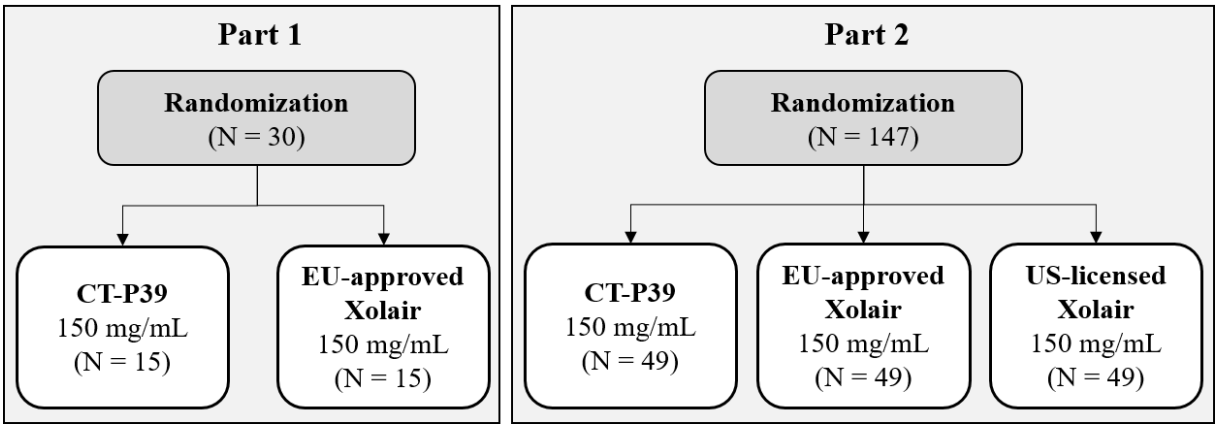
This study will be conducted in two parts in approximately 177 subjects. Subjects will be included in either of the parts of the study. The first 30 subjects will be assigned to Part 1 and the 147 subjects will be subsequently assigned to Part 2. Part 1 is a randomized, double-blind, two-arm, parallel group, single-dose study. The first 30 subjects will be enrolled in Part 1 to compare the initial safety and randomized in a 1:1 ratio to receive a single dose (150 mg) of CT-P39 or EU-approved Xolair. Part 2 is a randomized, double-blind, three-arm, parallel group, single-dose study. Approximately 147 subjects will be subsequently enrolled in Part 2 to demonstrate PK similarity and randomized in a 1:1:1 ratio to receive a single dose (150 mg) of CT-P39, EU-approved Xolair, or US-licensed Xolair. All subjects in Part 1 and Part 2 will undergo the same assessments. However, each part will be conducted independently, and data for each part will be analyzed and presented separately. The result of Part 1 will not affect the progression into Part 2.

A study drug will be administered subcutaneously via pre-filled syringe (PFS) on Day 1 and subjects will be followed up for 127 days for PK, PD, safety, and immunogenicity assessments. Subjects will be stratified by body weight (<70 kg *versus* ≥70 kg), serum total immunoglobulin E (IgE) level (<40 IU/mL *versus* ≥40 IU/mL), and sex (male *versus* female) as a part of the randomization for balanced distribution. Subjects will be admitted to the

study clinic on Day -1 and will be discharged on Day 4 after completion of the 72-hour assessments after study drug administration. The duration of in-house stay can be extended at the investigator's decision. The subsequent visits will be carried out on outpatient basis up to Day 127 (end-of-study [EOS]).

A scheme of the study design is presented in **Figure S1**.

Figure S1: Study Design



Abbreviations: EU = European Union; US = United States.

Investigational Medicinal Product(s):

Test Investigational Product, Strength(s), Formulation/Dosage Form:

CT-P39: 150 mg/mL, Solution for injection in PFS

Reference Investigational Products, Strength(s), Formulation/Dosage Form:

EU-approved Xolair: 150 mg/mL, Solution for injection in PFS

US-licensed Xolair: 150 mg/mL, Solution for injection in PFS

Dose and Route of Administration:

Each subject will receive a single dose of 150 mg of CT-P39, EU-approved Xolair, or US-licensed Xolair via PFS. The injection will be administered subcutaneously in the outer upper arm.

Number of Subjects:

Overall approximately 177 subjects will be enrolled in this study, 30 subjects in Part 1 and 147 subjects in Part 2.

The first 30 subjects will be enrolled in Part 1 and randomized (1:1) into 2 study arms as follows;

- Arm 1 (N=15): CT-P39
- Arm 2 (N=15): EU-approved Xolair

Subsequently, 147 subjects will be enrolled in Part 2 and randomized (1:1:1) into 3 study arms as follows;

- Arm 1 (N=49): CT-P39
- Arm 2 (N=49): EU-approved Xolair
- Arm 3 (N=49): US-licensed Xolair

Study Population:

Healthy subjects (male or female), 18 to 55 years (both inclusive) of age with a total IgE level of ≤100 IU/mL, a body weight of >40 and ≤90 kg, and a body mass index (BMI) between 18.0 and 32.0 kg/m^2 (both inclusive) are planned for enrollment.

Inclusion Criteria:

Subjects who meet the following criteria will be considered eligible to participate in the clinical study:

1. Healthy subject (male or female) between the ages of 18 and 55 years (both inclusive) (healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination,

including blood pressure [BP] and heart rate [HR] measurement, 12-lead electrocardiogram [ECG] and clinical laboratory tests prior to the study drug administration).

2. Subject with a body weight of >40 kg and ≤90 kg and a BMI between 18.0 kg/m^2 and 32.0 kg/m^2 (both inclusive).
3. Subject with a total IgE level of ≤100 IU/mL at screening.
4. Subject is able to understand and to comply with protocol requirements, instructions, and restrictions.
5. Subject voluntarily agrees to participate in this study and has given a written informed consent prior to undergoing any of the screening procedures.
6. Subject and their partner of childbearing potential must agree to use a highly effective method of contraception throughout the study as specified in Section 5.7.2. A man or woman is of childbearing potential if, in the opinion of the investigator, he or she is biologically capable of having children and is sexually active.

Exclusion Criteria:

Subjects who meet one or more of the following criteria will not be considered eligible to participate in the clinical study:

1. Current presence of allergic reaction such as asthma, urticaria, angioedema, and eczematous dermatitis considered as clinically significant.
2. History of anaphylactic shock or hypersensitivity including known or suspected clinically relevant drug hypersensitivity to any components of the test and reference drugs formulation or other similar drug (e.g., monoclonal antibodies and human intravenous immunoglobulin).
3. History of allergic reactions or sensitivity to latex or latex derived products.
4. History of and/or concomitant immune complex disease (including Type III hypersensitivity), hyperimmunoglobulin E syndrome, autoimmune disease, or bronchopulmonary aspergillosis.
5. Current parasitic infection or colonization on stool evaluation for ova and parasites (stool ova and parasite examination should be performed in subjects who meet following both criteria):
   (1) Correspond to any of risk factors for parasitic disease;
      - travel within 6 months prior to the study drug administration to or living in an endemic area;
      - chronic gastrointestinal symptoms;
      - chronic immunosuppression.
   (2) Absolute eosinophil count >2 x upper limit of normal.
6. History of and/or current medical condition including cardiac, gastrointestinal, renal, hepatic, hematological (including pancytopenia, aplastic anaemia or blood dyscrasia), metabolic (including known diabetes mellitus), neurologic or pulmonary diseases, or psychiatric condition classed as clinically significant by the investigator.
7. History or any concomitant active malignancy except adequately treated squamous or basal cell carcinoma of the skin.
8. A known infection with human immunodeficiency virus, hepatitis B or hepatitis C or any active infection requiring treatments, except adequately treated and completely recovered past infections.
9. History of and/or current illness within 28 days prior to the study drug administration that is identified as clinically significant by the investigator.
10. History of surgical intervention or an operation within 28 days prior to the study drug administration or planned to have surgical procedure during the study period.
11. History of and/or concurrent use of prescription medications (excluding hormonal birth control), over-the-counter drugs, dietary supplements or herbal remedies from 7 days or 5 half-lives (whichever is longer) prior to the study drug administration until the completion of the study.

12. Treatment with an investigational drug, any monoclonal antibody, fusion protein, or current use of biologics or participated in another clinical trial within 3 months or 5 half-lives (whichever is longer) prior to the study drug administration.
13. History of and/or concurrent treatment with an anti-IgE monoclonal antibodies, or any other antibody or protein targeting the IgE.
14. Female subject is pregnant or lactating or planning to be pregnant or to breastfeed or male subject is planning to father a child or donate sperms during the study period.
15. Subject has reasonable evidence or history of drug/alcohol/nicotine abuse prior to the study drug administration;
    (1) Positive result for drug urine test during screening or Day -1;
    (2) History or presence of regular consumption exceeding an average weekly intake of >14 units of alcohol in recent 3 months prior to the study drug administration (a standard unit is equal to approximately 285 mL of full strength beer [4.8% alcohol by volume {ABV}], 30 mL of spirits [40% ABV], or 100 mL of wine [13.5% ABV]);
    (3) Consume more than 10 cigarettes or equivalent per day within 28 days prior to the study drug administration.
16. Subject is unwilling to avoid the use of alcohol or alcohol-containing foods, medications, or beverages within 24 hours prior to each study visit throughout the study and/or unable to refrain from smoking during in-house stays.
17. Subject donated whole blood or lost 450 mL or more blood within 8 weeks (plasma/platelets donation within 4 weeks) prior to the study drug administration.
18. Subject with evidence of a condition (psychological, emotional problems, any disorders or resultant therapy) that is likely to invalidate informed consent, or with a limited ability to comply with the protocol requirements in the opinion of the investigator.
19. Subject is vulnerable (e.g., employees of the clinical trial site or any other individuals involved with the conduct of the study or immediate family members of such individuals, persons kept in prison, or other institutionalized persons by law enforcement).
20. Subject has the presence of tattoos, sunburn, or other skin disturbances (i.e., cuts, bruises, redness, hardness, tenderness etc.) on both the left and right upper arm which may interfere with a medical assessment of the injection site both prior to and following study drug administration.
21. Subject is not likely to complete the study for whatever reason in the opinion of the investigator.

Study Procedures:

Screening (Day -28 to Day -2):

Subjects will sign the informed consent and undergo procedures to determine eligibility. The total IgE level will be analyzed to confirm the eligibility with a validated immunoassay. Adverse events (AEs) and prior medications, and restriction assessment results will be monitored from the date when the informed consent form is signed.

Admission (Day -1):

Once pertaining tests and assessments for enrollment have been concluded to confirm the eligibility during screening period, the subjects will be admitted to the clinical unit on Day -1 for procedures to be performed for remaining eligibility tests.

Eligible subjects will undergo baseline assessments: re-check of inclusion and exclusion criteria, medical and medication history, body weight, check for drug abuse including nicotine and alcohol, vital signs, clinical laboratory tests including complement (C3 and C4) and total hemolytic complement test, physical examination, restriction assessment, collection of information related to AEs, prior medications, and urine pregnancy test in women of childbearing potential.

Study Period (Day 1 [Week 0] to Day 126 [Week 17]):

All subjects eligible will be randomized to one of treatment groups and a single dose (150 mg) of CT-P39,

EU-approved Xolair, or US-licensed Xolair will be administered to subjects on Day 1. Subjects will be confined to the clinical unit until completion of 72-hour assessments after study drug administration. The duration of in-house stay can be extended at the investigator's decision. The subsequent study visits will be carried out on outpatient basis.

Serum samples for PK, PD, and immunogenicity analyses will be obtained at pre-defined time points. Safety assessments including clinical laboratory tests, vital sign measurements, hypersensitivity/allergic reaction/injection site reaction monitoring, local site pain using 100 mm visual analogue scale (VAS), ECG, and physical examination will be performed. Adverse events, concomitant medication information, and adherence to restriction will be monitored throughout the study. Pre-defined time points for all assessments will be presented in Table 11-1.

End-of-Study Visit (Day 127 [Week 18]):

The EOS visit will be performed on Day 127. Subjects will return to the clinical unit and undergo the following assessments: PK, PD, clinical laboratory tests, immunogenicity assessments, collection of information related to AEs, concomitant medications, adherence to restriction, vital signs, body weight, ECG, physical examination, and pregnancy test in women of childbearing potential.

The total study duration from randomization will be up to 18 weeks for each individual subject who completes the entire clinical trial.

Criteria for Evaluation:

Primary Endpoints

The primary endpoints will be analyzed for the Part 2 subjects.

Pharmacokinetic parameters will be analyzed based on the concentrations of total omalizumab in the serum samples.

- Area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$)
- Area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-}last}$)
- Maximum serum concentration (C_{max})

Secondary Endpoints

The secondary endpoints will be analyzed for Part 1 and Part 2, separately. Data for each part will be independently analyzed and presented.

Pharmacokinetics

- Time to C_{max} (T_{max})
- Terminal half-life ($t_{½}$)
- Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation ($\%AUC_{ext}$)
- Terminal elimination rate constant (λ_z)
- Apparent total body clearance (CL/F)
- Apparent volume of distribution during the terminal phase (V_z/F)

For Part 1,

- $AUC_{0\text{-}inf}$
- $AUC_{0\text{-}last}$
- C_{max}

Pharmacodynamics

For free IgE, following parameters will be calculated:

- Minimum serum concentration (C_{min})
- Time to C_{min} (T_{min})
- Maximum percentage decrease in serum free IgE concentration from screening (max % decrease)

For total IgE, following parameters will be calculated:

- C_{max}
- T_{max}
- Maximum percentage increase in serum total IgE concentration from screening (max % increase)

Safety

- Adverse events (including serious AEs [SAEs] and AEs of special interest [AESIs])
- Hypersensitivity monitoring (including monitoring for Type III hypersensitivity)
- Injection site reaction monitoring
- Vital sign measurements (BP, HR, body temperature [BT], and respiratory rate [RR])
- Physical examination findings
- Clinical laboratory test results including hematology, chemistry, and urinalysis
- Twelve-lead ECG results
- Local injection site pain (using 100 mm VAS)

Immunogenicity

- Incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs).

Sample size assumption:

Overall, a total of approximately 177 subjects will be enrolled in this study.

For Part 1, approximately 30 healthy subjects will be randomized to receive either CT-P39 or EU-approved Xolair. A sample size justification based on a formal statistical hypothesis is not relevant for Part 1, hence a formal statistical inference will not be made.

For Part 2, 126 subjects (42 in treatment group) with evaluable data in the primary PK Set provide 90% statistical power to show that the 90% confidence interval (CI) for the ratio of geometric means of PK parameters (CT-P39 to EU-approved Xolair, CT-P39 to US-licensed Xolair, and EU-approved Xolair to US-licensed Xolair) lies within equivalence margins of 80% to 125% assuming that the coefficient of variation (CV) is 30% and the expected ratio is 1.03. The sample size is calculated from two one-sided tests with each at 5% significance level. Accounting for 15% of randomized subjects excluded from the PK Set, approximately 147 subjects (49 in each group) will be randomized to achieve the required sample size of 42 per group.

Statistical Methods:

Statistical analyses will be carried out independently for each part and the primary PK endpoints will be analyzed only for Part 2 subjects. To report the initial safety, PK, PD, and immunogenicity results, data up to Day 29 will be analyzed in Part 1.

The randomization code for each part will be broken for reporting purposes, respectively. The first code break will occur for subjects in Part 1 after the database lock for the data up to Day 29 of the last subject in Part 1 to report initial results. The second code break will occur for subjects in Part 2 after completion of the study. To perform the analyses of initial data from Part 1, unblinded personnel will be pre-defined and documented before breaking the study blind for Part 1. Part 1 will remain blinded to the investigators, subjects, pre-defined sponsor and contract research organization blinded teams until all subjects in both parts have completed the study and the database has been finalized for study termination. Regardless of code-breaking for Part 1, the subjects in Part 2 will maintain the blindness from the randomization until all subjects in both parts would complete the study and the database would be finalized for study termination.

Analysis Sets

Intent-to-treat (ITT) Set

The ITT Set is defined as all subjects enrolled and randomly assigned to receive a dose of the study drugs (CT-P39, EU-approved Xolair, or US-licensed Xolair), regardless of whether or not any study drug was administered. Subjects will be assigned to treatment groups based on randomization.

Pharmacokinetic (PK) Set

The PK Set is defined as all subjects who receive a complete dose of study drug (CT-P39, EU-approved Xolair, or US-licensed Xolair) and who have at least one post-treatment PK result with a concentration above the lower limit of quantification for omalizumab. Subjects will be analyzed according to the treatment they actually received. If any subject is found to be non-compliant with respect to dosing, a determination of the PK Set will be made on a case-by-case basis at the blinded Data Review Meeting before unblinding.

Pharmacodynamic (PD) Set

The PD Set is defined as all subjects who receive a complete dose of study drug (CT-P39, EU-approved Xolair, or US-licensed Xolair) and who have at least one post-treatment PD result. Subjects will be analyzed according to the treatment they actually received.

Safety Set

The Safety Set is defined as all randomly assigned subjects who receive a full or partial dose of study drug (CT-P39, EU-approved Xolair, or US-licensed Xolair). Subjects will be assigned to treatment groups based on treatment actually received.

Pharmacokinetic analysis

Pharmacokinetic analysis will be performed on the PK Set. The PK endpoints will be calculated using non-compartmental methods. The PK primary endpoint will be analyzed in subjects of Part 2. The statistical analysis of the log-transformed primary endpoints ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}) will be based on an analysis of covariance model with treatment as a fixed effect and body weight, total IgE level, and sex as covariates. Final determination of covariates and details will be described in the SAP. The similarity of PK between CT-P39 *versus* EU-approved Xolair, CT-P39 *versus* US-licensed Xolair, and EU-approved Xolair *versus* US-licensed Xolair will be concluded if the 90% CIs of the ratios of geometric means of each comparison are entirely contained within 80% to 125% for $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}. Back transformation will provide the ratio of geometric means and 90% CIs for these ratios.

Secondary endpoints ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max} for Part 1 and T_{max}, $t_{½}$, $\%AUC_{ext}$, λ_z, CL/F, and V_z/F for both parts) will be independently analyzed for each part.

Graphical presentations of PK data and additional PK parameters may be added at the discretion of the PK scientist, as appropriate. Pharmacokinetic parameters will be presented in listings and summarized in tables by treatment group. The tables will display the following descriptive statistics: number of subjects, mean, standard deviation (SD), median, minimum, maximum, the geometric mean and CV.

Pharmacodynamic analysis

Pharmacodynamic analysis will be performed on the PD Set. Descriptive statistics for all PD endpoints will be provided by treatment group including the number of subjects, mean, SD, median, minimum, maximum, geometric mean and CV.

Safety analysis

All safety analyses will be conducted on the Safety Set. The safety data will be listed and summarized by treatment group. The number and percentage of subjects who experienced AEs will be summarized by treatment group using system organ class and preferred term (PT). Adverse events will be summarized by severity and relationship to study drug. Serious adverse events will be summarized separately. Severity grading of AEs will be recorded based on National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. All reported terms for AEs will be coded using the Medical Dictionary for Regulatory Activities. Prior and concomitant medication will be coded using the World Health Organization Drug Dictionary. These medications will be summarized by drug class and preferred term. All safety data will be analyzed descriptively.

Immunogenicity analysis

Immunogenicity analyses will be conducted on the Safety Set. The number and percentage of subjects with ADA and NAb results will be presented by treatment group and visit.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
$\%AUC_{ext}$	Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation
ABV	Alcohol by volume
ADA	Anti-drug antibodies
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time zero to infinity
$AUC_{0\text{-}last}$	Area under the concentration-time curve from time zero to the last quantifiable concentration
BMI	Body mass index
BP	Blood pressure
BT	Body temperature
CI	Confidence interval
CIU	Chronic idiopathic urticaria
CL/F	Apparent total body clearance
C_{max}	Maximum serum concentration
C_{min}	Minimum serum concentration
CRO	Clinical research organization
CSR	Clinical study report
CSU	Chronic spontaneous urticaria
CV	Coefficient of variation
DMP	Data management plan
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End-of-study
EU	European Union
FcεRI	High-affinity IgE receptor
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second

GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
HREC	Human Research Ethics Committee
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IgE	Immunoglobulin E
ITT	Intent-to-treat
λ_z	Terminal elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OTC	Over-the-counter drug
PD	Pharmacodynamic(s)
PFS	Pre-filled syringe
PK	Pharmacokinetic(s)
PT	Preferred term
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SmPC	Summary of product characteristics
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to C_{max}
T_{min}	Time to C_{min}
ULN	Upper limit of normal (laboratory range)
US	United States

USPI	United States Prescribing Information
VAS	Visual Analogue Scale
V_z/F	Apparent volume of distribution during the terminal phase

1. INTRODUCTION

1.1 Background

Omalizumab is a recombinant deoxyribonucleic acid (DNA)-derived humanized monoclonal antibody of approximately 149 kiloDaltons in mass binds to human immunoglobulin E (IgE). Immunoglobulin E is an antibody produced in plasma cells, which functions in Type I hypersensitivity and can be found on mast cells, basophils, and dendritic cells. When IgE binds to an Fc receptor, the receptor becomes primed to bind with a foreign antigen, and when bound leads to degranulation of the host cells. When granulation occurs, a large number of mediators including various cytokines (primarily interleukins), histamine, eicosanoids (including prostaglandins, leukotrienes, and thromboxanes), and platelet activating factor are released which yield beneficial immune functions, but can also be associated with disease states in elevated amounts. As IgE is known to be elevated in a number of allergy related diseases including sinusitis, rhinitis, food allergies, chronic urticaria, atopic dermatitis, and allergic asthma, pharmacological interventions targeting IgE have been explored as a method for treating these conditions (Gould *et al*. 2003).

Omalizumab specifically binds to free IgE in the blood, as well as membrane-bound IgE, however it does not bind to high-affinity IgE receptor (FcεRI)-bound IgE. By binding to IgE, omalizumab inhibits the binding of antigens to IgE, which inhibits the granulation process. This action in turn inhibits the release of the various mediators released via granulation, and as such functions to lessen sensitivity to allergens (Xolair United States Prescribing Information [USPI] 2019, Xolair Summary of Product Characteristics [SmPC] 2019).

Xolair, biological medicinal product containing the active ingredient omalizumab, was approved in 2003 in the United States (US) and European Union (EU). In the US, Xolair is approved for use in patients with moderate to severe persistent asthma who do not receive adequate benefit from inhaled corticosteroids (in patients aged 6 and older) and also in patients with chronic idiopathic urticaria (CIU) who do not receive adequate benefit from antihistamine treatment (in patients aged 12 and older). In the EU, Xolair is indicated as an add-on therapy for use in patients with convincing IgE mediated asthma (in patients aged 6 to 12, and also 12 and older when presenting with reduced lung function [forced expiratory volume in 1 second {FEV_1} <80%]) and also in patients with chronic spontaneous urticaria (CSU) (in patients aged 12 and older) (Xolair USPI 2019, Xolair SmPC 2019).

Xolair is formulated as a solution for injection, available in both vial and single-dose pre-filled syringe (PFS) formulations. The injection solutions are supplied as a sterile, preservative-free, clear to slightly opalescent and colorless to pale brownish-yellow solution. The PFS formulation of Xolair is available containing either 75 mg or 150 mg of omalizumab. The excipients of both PFS variants are identical, however the amounts are doubled in the 150 mg variant compared to the 75 mg variant. The 150 mg variant contains 150 mg of omalizumab in 1 mL of sterile water for injection, in which L-arginine hydrochloride (42.1 mg), L-histidine (1.37 mg), L-histidine hydrochloride monohydrate (2.34 mg), and polysorbate 20 (0.4 mg) are dissolved. For asthma, the recommended dosage varies between 75 mg to 375 mg by subcutaneous (SC) injection every 2 or 4 weeks in the US, and 75 mg to 600 mg by SC injection every 2 or 4 weeks in the EU,

depends on baseline IgE level and body weight. For CSU, the recommended dosage is 150 or 300 mg by SC injection every 4 weeks in the US, and 300 mg by SC injection every 4 weeks in the EU (Xolair USPI 2019, Xolair SmPC 2019).

CT-P39 is under development as a product containing omalizumab and is being developed as a biosimilar product of Xolair. Omalizumab, the active ingredient of CT-P39, is produced by similar recombinant DNA technology to the EU-approved and US-licensed forms of omalizumab, and utilizes a Chinese hamster ovary cell expression system and comparable purification process.

CT-P39 will be supplied in a PFS at a concentration of 150 mg/mL as a clear to slightly opalescent, colorless to pale brownish-yellow solution for SC administration. The CT-P39 drug product will have the same pharmaceutical form and strength as Xolair and is intended to have a highly similar quality profile to Xolair.

CELLTRION, Inc. plans to seek approval for all indications for which the original product has been approved by demonstrating similarity of CT-P39 with the original product, Xolair, through an extensive array of quality, nonclinical and clinical comparability assessments.

1.1.1 Non-Clinical Studies

Detailed information regarding the non-clinical pharmacology and toxicology of CT-P39 can be found in the investigator's brochure (IB).

1.1.2 Clinical Studies

No clinical studies of CT-P39 have been performed.

1.2 Rationale for the Clinical Study

CT-P39 is a monoclonal antibody currently being developed by CELLTRION, Inc., which is intended to be formulated as a biosimilar to Xolair. The purpose of Part 2 of this clinical study is to compare the pharmacokinetics (PK), pharmacodynamics (PD), safety, and immunogenicity of the proposed biosimilar test product (CT-P39) with reference products (EU-approved Xolair and US-licensed Xolair) after a single SC injection of 150 mg of each product to healthy adult subjects following the recommendations of the Food and Drug Administration (FDA) guidance "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (FDA 2015)", "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (FDA 2016)", and European Medicines Agency (EMA) guidance "Similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010)".

Part 1 is designed to evaluate the initial safety of CT-P39 up to Day 29, compared to that of EU-approved Xolair, which will accelerate development program of CT-P39. However, blinding of Part 2 will be maintained until the end-of-study (EOS) in order to avoid bias for the demonstration of the PK similarity.

Healthy subjects with a total IgE level of ≤100 IU/mL have been selected for this study in order to avoid potentially high variability of the exposure of omalizumab if administered to patients

with allergic asthma or CSU, which would introduce a bias into the attainment of the primary study objectives.

The dose of 150 mg omalizumab in CT-P39 and the two reference products has been selected as this is the dose recommended for patients in the weight range of >40 to ≤90 kg with a serum total IgE level of ≤100 IU/mL and because omalizumab PK is linear at across the dose range of 75 mg to 600 mg given as single SC dose (Xolair USPI 2019, Xolair SmPC 2019).

A parallel-group design will be used in this study to prevent potential crossover effects.

1.3 Risk-Benefit Assessment

Information about the risk following the administration of omalizumab was taken from the Xolair USPI (2019) and SmPC (2019) of US-licensed Xolair and EU-approved Xolair, respectively.

In view of the structural, biological, and toxicological similarity to Xolair, CT-P39 is expected to display a similar safety profile.

The proposed safety screening and monitoring assessments are deemed to be sufficient to monitor potential risks of CT-P39 administration. Since omalizumab will be administered only once at the approved dosage of 150 mg, the overall risk of the study for healthy subjects is considered to be acceptable. No therapeutic benefit from omalizumab treatment is intended for the healthy subjects in this study.

2. STUDY OBJECTIVES

2.1 Primary Objective

Part 2:

- To demonstrate PK similarity in terms of area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$), area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-}last}$), and maximum serum concentration (C_{max}) of CT-P39, EU-approved Xolair, and US-licensed Xolair in healthy subjects (CT-P39 to EU-approved Xolair, CT-P39 to US-licensed Xolair, and EU-approved Xolair to US-licensed Xolair).

2.2 Secondary Objective

Data for each part will be independently analyzed and presented.

Part 1:

- To evaluate initial safety up to Day 29 in terms of treatment-emergent adverse events (TEAEs) of CT-P39, compared to that of EU-approved Xolair in healthy subjects.
- To assess additional safety, PK, PD, and immunogenicity of CT-P39 and EU-approved Xolair in healthy subjects up to Day 29.

Both parts:

- To assess additional safety, PK, PD, and immunogenicity of CT-P39, EU-approved Xolair, and US-licensed Xolair in healthy subjects up to Day 127.

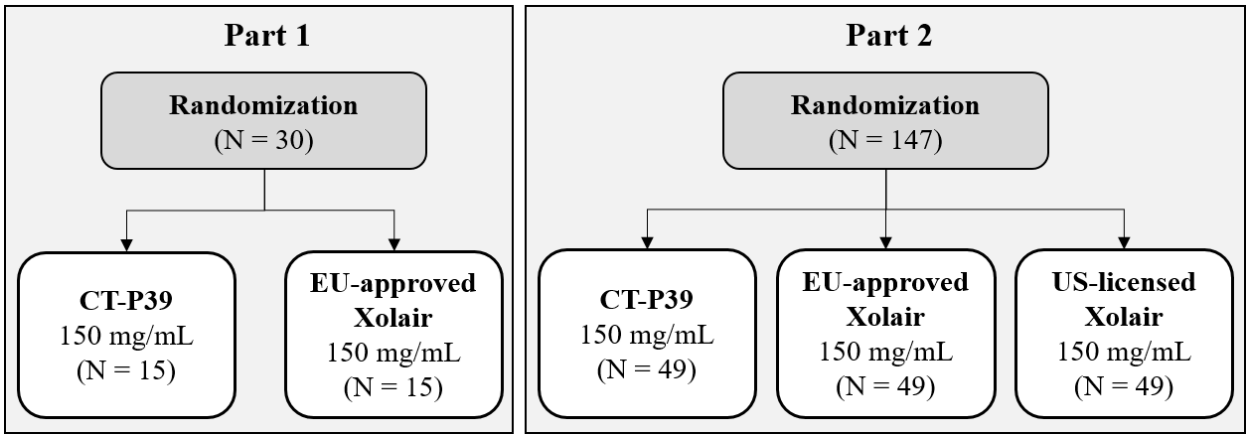
3. INVESTIGATIONAL PLAN

3.1 Overview

This study is a randomized, double-blind, 2-part, parallel, single-dose study, in healthy male and female subjects aged between 18 and 55 years (both inclusive). This study will be conducted in two parts in approximately 177 subjects. Subjects will be included in either of the parts of the study. The first 30 subjects will be assigned to Part 1 and the 147 subjects will be subsequently assigned to Part 2. Part 1 is a randomized, double-blind, two-arm, parallel group, single-dose study. The first 30 subjects will be enrolled in Part 1 to compare the initial safety and randomized in a 1:1 ratio to receive a single dose (150 mg) of CT-P39 or EU-approved Xolair. Part 2 is a randomized, double-blind, three-arm, parallel group, single-dose study. Approximately 147 subjects will be subsequently enrolled in Part 2 to demonstrate PK similarity and randomized in a 1:1:1 ratio to receive a single dose (150 mg) of CT-P39, EU-approved Xolair, or US-licensed Xolair. All subjects in Part 1 and Part 2 will undergo the same assessments. However, each part will be conducted independently, and data for each part will be analyzed and presented separately. The result of Part 1 will not affect the progression into Part 2.

A study drug will be administered subcutaneously via PFS on Day 1 and subjects will be followed up for 127 days for PK, PD, safety, and immunogenicity assessments. Subjects will be stratified by body weight (<70 kg *versus* ≥70 kg), serum total IgE level (<40 IU/mL *versus* ≥40 IU/mL), and sex (male *versus* female) as a part of the randomization for balanced distribution.

Figure 3-1: Study Design



Abbreviations: EU= European Union; US = United States.

Subjects will sign and date the informed consent form (ICF), and they will be screened for eligibility within 28 to 2 days prior to administration of the study drug.

Eligible subjects will be admitted to the clinical unit on Day -1 to undergo baseline assessments and will be randomized on Day 1 (prior to dosing) to one of the treatment arms to receive CT-P39, EU-approved Xolair, or US-licensed Xolair once all eligibility criteria have been confirmed. Subjects will be confined to the clinical unit until completion of the 72-hour assessments after study drug administration. The duration of in-house stay can be extended at the investigator's decision. The consecutive study visits will be carried out on an outpatient basis. Blood sample for

PK, PD and immunogenicity analysis will be collected up to Day 127. Safety will be assessed throughout the study by collection of information about adverse events (AEs) and concomitant medications, by clinical laboratory testing, measurement of vital signs, recording of 12-lead electrocardiogram (ECG), injection site monitoring, hypersensitivity monitoring, physical examination, local site pain assessment. An EOS examination will take place on Day 127.

The total duration of the participation will be up to 22 weeks for each individual subject who completes the entire clinical trial, including up to 4 weeks of screening period and 18 weeks of post-treatment follow-up assessments period.

Detailed procedures performed on each study day/visit are described in Section 6.1, Table 6-1, Table 6-2, Table 6-3, and Table 11-1.

3.2 Endpoints

3.2.1 Primary Endpoints

The primary endpoints will be analyzed for the Part 2 subjects.

Pharmacokinetic parameters will be analyzed based on the concentrations of total omalizumab in the serum samples.

- Area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$)
- Area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-}last}$)
- Maximum serum concentration (C_{max})

3.2.2 Secondary Endpoints

The secondary endpoints will be analyzed for Part 1 and Part 2, separately. Data for each part will be independently analyzed and presented.

Pharmacokinetics

- Time to C_{max} (T_{max})
- Terminal half-life ($t_{1/2}$)
- Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation ($\%AUC_{ext}$)
- Terminal elimination rate constant (λ_z)
- Apparent total body clearance (CL/F)
- Apparent volume of distribution during the terminal phase (V_z/F)

For Part 1,

- $AUC_{0\text{-inf}}$
- $AUC_{0\text{-last}}$
- C_{max}

Pharmacodynamics

For free IgE, following parameters will be calculated:

- Minimum serum concentration (C_{min})
- Time to C_{min} (T_{min})
- Maximum percentage decrease in serum free IgE concentration from screening (max % decrease)

For total IgE, following parameters will be calculated:

- C_{max}
- T_{max}
- Maximum percentage increase in serum total IgE concentration from screening (max % increase)

Safety

- Adverse events (including serious AEs [SAEs] and AEs of special interest [AESIs])
- Hypersensitivity monitoring (including monitoring for Type III hypersensitivity)
- Injection site reaction monitoring
- Vital sign measurements (blood pressure [BP], heart rate [HR], body temperature [BT], and respiratory rate [RR])
- Physical examination findings
- Clinical laboratory test results including hematology, chemistry, and urinalysis
- Twelve-lead ECG results
- Local injection site pain (using 100 mm visual analogue scale [VAS])

Immunogenicity

- Incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs)

4. STUDY POPULATION

The study population will consist of healthy male and female subjects, 18 to 55 years (both inclusive) of age with a total IgE level of ≤100 IU/mL, a body weight of >40 and ≤90 kg, and a body mass index (BMI) between 18.0 and 32.0 kg/m^2 (both inclusive). Subjects must be able to provide written informed consent and meet all the inclusion criteria and none of the exclusion criteria, according to the criteria outlined below (Sections 4.2 and 4.3).

4.1 Number of Subjects

Approximately 177 subjects will be enrolled in the clinical study in 2 parts: 30 subjects will be enrolled in Part 1 and randomized to 2-arms (CT-P39 or EU-approved Xolair) in a 1:1 ratio, and 147 subjects will be enrolled in Part 2 and randomized to 3-arms in a 1:1:1 ratio to receive a study drug (CT-P39, EU-approved Xolair or US-licensed Xolair).

4.2 Inclusion Criteria

Subjects who meet the following criteria will be considered eligible to participate in the clinical study:

1. Healthy subject (male or female) between the ages of 18 and 55 years (both inclusive) (healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including BP and HR measurement, 12-lead ECG and clinical laboratory tests prior to the study drug administration).
2. Subject with a body weight of >40 kg and ≤90 kg and a BMI between 18.0 kg/m^2 and 32.0 kg/m^2 (both inclusive).
3. Subject with a total IgE level of ≤100 IU/mL at screening.
4. Subject is able to understand and to comply with protocol requirements, instructions, and restrictions.
5. Subject voluntarily agrees to participate in this study and has given a written informed consent prior to undergoing any of the screening procedures.
6. Subject and their partner of childbearing potential must agree to use a highly effective method of contraception throughout the study as specified in Section 5.7.2. A man or woman is of childbearing potential if, in the opinion of the investigator, he or she is biologically capable of having children and is sexually active.

4.3 Exclusion Criteria

Subjects who meet one or more of the following criteria will not be considered eligible to participate in the clinical study:

1. Current presence of allergic reaction such as asthma, urticaria, angioedema, and eczematous dermatitis considered as clinically significant.

2. History of anaphylactic shock or hypersensitivity including known or suspected clinically relevant drug hypersensitivity to any components of the test and reference drugs formulation or other similar drug (e.g., monoclonal antibodies and human intravenous immunoglobulin).

3. History of allergic reactions or sensitivity to latex or latex derived products.

4. History of and/or concomitant immune complex disease (including Type III hypersensitivity), hyperimmunoglobulin E syndrome, autoimmune disease, or bronchopulmonary aspergillosis.

5. Current parasitic infection or colonization on stool evaluation for ova and parasites (stool ova and parasite examination should be performed in subjects who meet following both criteria):

   (1) Correspond to any of risk factors for parasitic disease;
   - travel within 6 months prior to the study drug administration to or living in an endemic area;
   - chronic gastrointestinal symptoms;
   - chronic immunosuppression.

   (2) Absolute eosinophil count >2 x upper limit of normal (ULN).

6. History of and/or current medical condition including cardiac, gastrointestinal, renal, hepatic, hematological (including pancytopenia, aplastic anaemia or blood dyscrasia), metabolic (including known diabetes mellitus), neurologic or pulmonary diseases, or psychiatric condition classed as clinically significant by the investigator.

7. History or any concomitant active malignancy except adequately treated squamous or basal cell carcinoma of the skin.

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

9. History of and/or current illness within 28 days prior to the study drug administration that is identified as clinically significant by the investigator.

10. History of surgical intervention or an operation within 28 days prior to the study drug administration or planned to have surgical procedure during the study period.

11. History of and/or concurrent use of prescription medications (excluding hormonal birth control), over-the-counter drugs (OTC), dietary supplements or herbal remedies from 7 days or 5 half-lives (whichever is longer) prior to the study drug administration until the completion of the study.

12. Treatment with an investigational drug, any monoclonal antibody, fusion protein, or current use of biologics or participated in another clinical trial within 3 months or 5 half-lives (whichever is longer) prior to the study drug administration.

13. History of and/or concurrent treatment with an anti-IgE monoclonal antibodies, or any other antibody or protein targeting the IgE.

14. Female subject is pregnant or lactating or planning to be pregnant or to breastfeed or male subject is planning to father a child or donate sperms during the study period.

15. Subject has reasonable evidence or history of drug/alcohol/nicotine abuse prior to the study drug administration;

    (1) Positive result for drug urine test during screening or Day -1;
    (2) History or presence of regular consumption exceeding an average weekly intake of >14 units of alcohol in recent 3 months prior to the study drug administration (a standard unit is equal to approximately 285 mL of full strength beer [4.8% alcohol by volume {ABV}], 30 mL of spirits [40% ABV], or 100 mL of wine [13.5% ABV]);
    (3) Consume more than 10 cigarettes or equivalent per day within 28 days prior to the study drug administration.

16. Subject is unwilling to avoid the use of alcohol or alcohol-containing foods, medications, or beverages within 24 hours prior to each study visit throughout the study and/or unable to refrain from smoking during in-house stays.

17. Subject donated whole blood or lost 450 mL or more blood within 8 weeks (plasma/platelets donation within 4 weeks) prior to the study drug administration.

18. Subject with evidence of a condition (psychological, emotional problems, any disorders or resultant therapy) that is likely to invalidate informed consent, or with a limited ability to comply with the protocol requirements in the opinion of the investigator.

19. Subject is vulnerable (e.g., employees of the clinical trial site or any other individuals involved with the conduct of the study or immediate family members of such individuals, persons kept in prison, or other institutionalized persons by law enforcement).

20. Subject has the presence of tattoos, sunburn, or other skin disturbances (i.e., cuts, bruises, redness, hardness, tenderness, etc.) on both the left and right upper arm which may interfere with a medical assessment of the injection site both prior to and following study drug administration.

21. Subject is not likely to complete the study for whatever reason in the opinion of the investigator.

4.4 Subject Withdrawal and Replacement

Subjects will be withdrawn from the study prematurely for the following reasons:

- Withdrawal of consent: Subjects have the right to withdraw from the study at any time for any reason.
- Protocol violation of concern: The subject will be withdrawn by the investigator after discussion with CELLTRION, Inc.
    - If protocol violations that may affect study objectives occur, or
    - If it is discovered that the subject has entered the study in violation of the protocol.

- If subject dies.
- If subject is pregnant.
- Adverse event: If a subject reports symptoms that are considered unacceptable by the investigator and/or CELLTRION, Inc., he or she will be withdrawn from the study. The appropriate AE page in electronic case report form (eCRF) is to be completed.

If premature withdrawal occurs for any reason, the investigator must determine the primary reason for a subject's premature withdrawal from the study and record this information in the eCRF.

Subjects who discontinue the study after administration of study drug will be asked to participate in the safety assessments of the EOS procedures including a physical examination, vital sign measurements, 12-lead ECG and standard safety laboratory tests, if possible. All subjects who withdraw from the study because of an AE or clinical laboratory abnormality will be followed up at suitable intervals in order to evaluate the course of the AE or laboratory abnormality and to ensure resolution or stabilization of the event. The subsequent outcomes of these events will be recorded in the eCRF.

For subjects who are lost to follow-up (i.e., those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show due diligence by documenting in the source documents steps taken to contact the subjects, e.g., dates of telephone calls, registered letters, etc. Subjects who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. The status of subjects who fail to complete final assessments will be documented in the eCRF.

For screen failed subjects, rescreen will be allowed only after receiving ICF again with new screening number; subjects withdrawn (after randomization) but prior to the study drug administration will be replaced. However, subjects withdrawn after the study drug administration will not be replaced.

5. STUDY TREATMENTS

5.1 Investigational medicinal product

5.1.1 Identity of the Investigational Medicinal Products

The study drugs that will be used in this study are outlined in Table 5-1.

Table 5-1: Identity of Investigational Products

Study drug name	Dosage form	Strength	Route
CT-P39	Solution for injection in PFS	150 mg	SC
EU-approved Xolair	Solution for injection in PFS	150 mg	SC
US-licensed Xolair	Solution for injection in PFS	150 mg	SC

Abbreviations: EU = European Union; PFS = Pre-filled syringe; SC = subcutaneous; US = United States.

5.1.2 Supply, Packaging, Labeling and Storage

The study drug (CT-P39, EU-approved Xolair and US-licensed Xolair) will be supplied by CELLTRION, Inc. The study drug will be packaged and labeled according to applicable local and regulatory requirements.

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

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

All study drug supplies must be stored in accordance with the manufacturer's instructions and will be stored in a refrigerator at 2℃ to 8℃ and will not be frozen. The immediate containers must be kept in the outer carton until use to protect the study drug from light. Until dispensed to

the subjects, the study drugs will be stored in a securely locked area, accessible to authorized personnel only.

5.1.3 Drug Accountability, Dispensing and Destruction

It is the responsibility of the clinical investigator to ensure that all study drug received at the study center will be inventoried and accounted for throughout the study and the result recorded in the drug accountability form maintained at the study center. The drug accountability will be verified by the monitor during on-site monitoring visits. In addition to the amount required for the study, an appropriate number of dosage units of the test and reference products must also be sent to the clinical sites for drug retention purposes. Clinical sites will store the retention samples on site for a minimum of 5 years following the application approval or, if not approved, at least 5 years after the completion of the study (in accordance with FDA Code of Federal Regulations Title 21), unless documented by CELLTRION, Inc. that the study will not be submitted to the FDA. Retention samples can be stored at the independent 3rd party depot after end of the study.

The investigator agrees not to supply the study drug to any person other than sub-investigators, delegated staff, and the subjects participating in the study. Study drug may not be relabeled or reassigned for use by other subjects unless approved by CELLTRION, Inc.

During the study, unused study drug syringes should be returned to the depot of origin. Accountability of the product must be completed at the site level and discrepancies, if any, need to be resolved prior to return. Only if it is written in standard operating procedures (SOPs) or documentation in place, the used PFS can be destroyed locally. The list of destroyed PFS must be recorded. The investigator agrees to neither dispense the study drug from, nor store it at, any study center other than the study centers agreed upon with CELLTRION, Inc.

Details in study drugs accountability and destruction will be followed according to the pharmacy manual.

5.2 Method of Assigning Subjects to Treatment Group

5.2.1 Screening Numbers

All screened subjects will be assigned unique screening or run-in numbers. These numbers will be used to identify subjects during study period.

5.2.2 Randomization

Randomization will occur at Day 1 after eligibility for the study has been confirmed. For both study parts, subjects will be randomly assigned to treatment groups (1:1 ratio of CT-P39 or EU-approved Xolair for Part 1 and 1:1:1 ratio of CT-P39, EU-approved Xolair or US-licensed Xolair for Part 2). The randomization will be stratified by body weight (<70 kg *versus* ≥70 kg), serum total IgE level (<40 IU/mL *versus* ≥40 IU/mL), and sex (male *versus* female) as a part of the randomization for balanced distribution.

5.3 Administration of Study Drug

On Day 1, a subject will receive a single SC injection of CT-P39, EU-approved Xolair, or US-licensed Xolair. The injection will take place under consideration of dietary and fluid restrictions (Section 5.7.1).

The PFS will be taken out of the refrigerator and allowed to reach room temperature (approximately 25 ℃) before preparing it for injection. The expected timeframe to acclimatize should be approximately 20 minutes, however additional time may be required if acclimatization takes longer. During this time, the syringe should be kept in its storage box to protect it from light. The timeframe that the syringe is maintained at room temperature should not exceed 4 hours to ensure maximal stability of the study drug.

The study drug will be administered in subjects to the clean and intact outer upper arm area on the subject's non-dominant side (i.e., left upper arm for a right-hand dominant subject, and vice versa). If a medical officer, or other delegated clinical staff member, deems that the participants' non-dominant upper arm area is unsuitable for study drug administration (i.e., presence of a tattoo, sunburn, or other skin disturbance) which impedes the ability to make a post-dose assessment of the injection area, the dominant upper arm may be used as a secondary administration location. The study drug injection site will be recorded in the source data and eCRF for each participant.

The injection site will be washed with an alcohol pad in a circular motion and let it air dry for 10 seconds. The subjects will be residing in a semi-recumbent position while they receive the study drug injection and for 2 hours after. The study drug will be administered by the site-qualified and trained clinical staff member(s) (e.g., nurse/physician, etc.), who is designated as unblinded site personnel. When administering the study drug, the designated clinical staff member will gently pinch the skin of the upper arm, insert the needle fully at an angle between 45° to 90° , depress the plunger fully, withdraw the needle with the plunger depressed, release the plunger, and then dispose the used syringe in accordance with the pharmacy manual. By exception, the subjects may get up (e.g., toilet visit) following study drug administration, but they must be instructed to request the clinical staff for assistance.

In the event that a subjects withdraw consent, when feasible, they should be followed up for safety given by the study design after they have received the study drug.

5.4 Treatment Compliance

The study drug administration will be performed by site-qualified and trained personnel. The date and time of the study drug administration will be documented, and complete administration of entire dose will be confirmed and recorded. Comments will be recorded if there are any deviations from the planned dosing procedures.

5.5 Blinding and Breaking the Blind

The study will be performed in a double-blind manner. The randomization codes will not be revealed to study subjects, investigators, or study center personnel except for the pre-defined unblinded personnel.

Pharmacy personnel (trained by a delegated pharmacist) at the clinical sites who has no other subject contact and who are not directly involved with the clinical aspects of the study will prepare and dispense the study medication and will be aware of the randomization code. All study drugs will be delivered to the clinical sites in the form of a PFS and will be assigned to treatment arms by the pharmacy personnel in accordance with the provided randomization schedule. All study drugs will be supplied to the trained clinical staff member in a sealed carton marked with the subject's screening number.

As the presentation of the three study drugs are not identical in visual appearance, the trained clinical staff member(s) responsible for drug administration (e.g., nurse/physician, etc.) will be designated as unblinded site personnel and will not be involved in any clinical or safety evaluations that are part of the blinded protocol or have other subject contact. Subjects will be blinded through the use of a blindfold, screen or similar method during the dosing procedure so that the injection syringe will not be visible to subject. Blinded staff will be absent during injection and remain blinded throughout the study.

Under normal circumstances, the blind should not be broken. The blind should be broken if specific emergency treatment would be dictated as knowing the study drug assignment is required for medical management. In such cases, the investigator may, in an emergency, determine the identity of the study drug. If suspected unexpected serious adverse reactions (SUSARs) occur, which are subject to expedited reporting, the blind should be broken before submission to the competent authorities, if required. If the blind is broken, the date, time and reason for the unblinding must be documented in the appropriate filed of the eCRF and the medical monitor and/or the sponsor will be informed as soon as possible. Any subjects for whom the blind is broken may continue in the study.

The overall randomization code for each part will be broken for reporting purposes, respectively. The first code break will occur for subjects in Part 1 after the database lock for the data up to Day 29 of the last subject in Part 1 to report initial results. The second code break will occur for subjects in Part 2 after completion of the study. To perform the analyses of initial data from Part 1, unblinded personnel will be pre-defined and documented before breaking the study blind for Part 1. Part 1 will remain blinded to the investigators, subjects, pre-defined sponsor and contract research organization (CRO) blinded personnel until all subjects in both parts have completed the study and the database has been finalized for study termination. Regardless of code-breaking for Part 1, the subjects in Part 2 will maintain the blind from the randomization until all subjects in both parts have completed the study and the database has been finalized for study termination.

5.6 Prior, Concomitant, and Prohibited Medications

Information (e.g., drug name, date[s] of administration, etc.) about prior medications taken by the subject within 30 days before he or she signs the ICF (inclusive of the applicable periods for prohibited medications as defined in Section 4.3) will be recorded in both the source documents and eCRF.

Subjects who have any history of treatment with anti-IgE monoclonal antibodies, or any other antibody or protein targeting IgE must be excluded. Treatment with an investigational drug, any

monoclonal antibody, fusion protein, or current use of a biologic or participated in another clinical trial within 3 months or 5 half-lives (whichever is longer) prior to the study drug administration is prohibited. The use of prescription medications (excluding hormonal birth control), OTC, dietary supplements or herbal remedies within 7 days or 5 half-lives (whichever is longer) prior to the study drug administration until EOS will not be permitted.

Concomitant medication use will be recorded from the time the subject signs the ICF until the EOS visit. Concomitant medication use is permitted if indicated by the investigator for premedication or treatment of an AE.

Prohibited medications during the study include the following:

- Monoclonal antibody or fusion protein, or other biologic agent
- Any other investigational drug except for the study drug used during this study
- Over-the-counter drugs, prescription medications (excluding hormonal birth control), dietary supplements, or herbal remedies excluding the premedications or treatments of AEs

It is the investigator's responsibility to ensure that details regarding the medication are adequately recorded in both the source documents and eCRF. Any changes in concomitant medications will also be recorded in both the source documents and eCRF.

5.7 Restrictions

5.7.1 Dietary and Fluid Restrictions

Alcohol: Alcohol containing products (including alcohol, alcohol-containing foods, medications, or beverages) must be avoided from 24 hours before any study visit and while subjects are confined to the study center. Subjects will abstain from alcohol-containing products for 24 hours prior to each PK sampling time point. Subject will not exceed an alcohol consumption of 14 units per week until the end of the study period. One standard unit is equal to approximately 285 mL of full strength beer (4.8% ABV), 30 mL of spirits (40% ABV), or 100 mL of wine (13.5% ABV). An alcohol breath test will be performed at screening and on Day -1.

Caffeine: Subjects will not be permitted to drink caffeine or xanthine-containing products (e.g., coffee, black tea, cola, etc., or use caffeine or xanthine-containing products) for 24 hours prior to the study drug administration and during the confinement period of the study. Subjects will abstain from caffeine or xanthine-containing products for 24 hours prior to each PK sampling time point.

Nicotine: Subjects will be permitted to smoke less than 10 cigarettes or equivalent per day until the end of the study period, but will not be allowed to smoke during the confinement period of the study.

Meals: Subjects must abstain from all food and drink (except water) at least 8 hours prior to the study drug administration and at least 4 hours prior to any safety laboratory evaluations. Water is permitted until 1 hour prior to the study drug administration and may be consumed without restriction beginning 1 hour after the study drug administration. No outside food or drink is permitted at the study center. All meals will be provided by the study center.

The investigator, or delegated clinical staff member, will check if subject is complying with these restraints during the study.

5.7.2 Other Restrictions

Activity: Strenuous activity (e.g., heavy lifting, weight training, calisthenics, and aerobics) is prohibited from 96 hours prior to admission until discharge. After discharge, mild physical activity can be resumed, but strenuous physical activity is prohibited 96 hours prior to each study visit.

Medications: Restrictions on medication during the study is described in Section 5.6.

Contraception: Subjects and their partners of childbearing potential must agree to use a highly effective method of contraception throughout the study. If a subject withdraws from the study after the study drug administration, the subject and their partner of childbearing potential must use a highly effective method of contraception for 3 months after the study drug administration. A highly effective method of birth control may be defined as those which result in a low failure rate (e.g., <1% per year, when used consistently and correctly). Examples of acceptable forms of highly effective contraception for females include: abstinence, simultaneous use of hormonal contraceptives starting at least 4 weeks prior to study drug administration and must agree to use the same hormonal contraceptive throughout the study and condom for the male partner, simultaneous use of intra-uterine contraceptive device placed at least 4 weeks prior to study drug administration and condom for the male partner, or a sterilized male partner (vasectomized since at least 6 months). Examples of acceptable forms of highly effective contraception for males include: abstinence, simultaneous use of a male condom and, for the female partner, hormonal contraceptives (used since at least 4 weeks) or intra-uterine contraceptive device (placed since at least 4 weeks). Examples of non-acceptable methods of contraception include solo use of a barrier method (including use of a diaphragm, cervical cap, or condom), periodic abstinence, the withdrawal method, or use of spermicide. Subjects are not permitted to donate sperm or plan to have a child during the study (at least 3 months after the study drug administration for withdrawn subject). For female subjects with same sex partners exclusively, no contraceptive use is required. For male subjects with same sex partners exclusively, use of condoms is recommended.

The investigator, or delegated clinical staff member, will check if subject is complying with these restraints during the study.

6. STUDY ASSESSMENTS AND PROCEDURES

Before performing any study procedures, all potential subjects will sign and date an ICF. The investigator will address all questions raised by the subject before the subject signs the ICF. The investigator will also sign and date the ICF.

Subjects will undergo study procedures at the time points specified in the Schedule of Assessments (Table 11-1). Study procedures can be performed within the given tolerance window, which is the allowed flexibility range without protocol violation. Even if an assessment takes place using the given tolerance window, the consecutive assessment will be performed from the baseline time point.

All clinical or safety assessments will be performed by the blinded staff.

6.1 Assessments by Visit

6.1.1 Screening Visit (Days -28 to -2)

All screening assessments will be the same for subjects in all parts of the study (unless otherwise indicated).

Potential subjects for the inclusion in the study will be asked to attend the screening visit fasting apart from water (duration of the fast approximately 4 hours). Written informed consent will be obtained from all subjects before any screening procedures are performed. Subjects will be fully informed of their responsibilities (in terms of attending the study visits, dietary and lifestyle restrictions) of all the procedures expected to be performed in the study, the possible risks and disadvantages of being dosed with omalizumab and their rights while participating in the study. They will have the opportunity to ask questions and have time to consider participation. If the subject wishes to participate in the study, they will be asked to sign and date the ICF.

If more tests or assessments are required to check the subject's eligibility for study participation, a subject may be invited to additional visits within the screening period at the discretion of the investigator.

During the screening visit, the following evaluations will be performed:

- Obtain written informed consent
- Medical and medication history
- Demographics: race, ethnicity, sex, age (years)
- Review inclusion/exclusion criteria
- Body height (cm), weight (kg), and BMI (kg/m^2)
- Physical examination
- Serology tests (Hepatitis B surface antigen [HBsAg], anti-hepatitis C virus [anti-HCV], and HIV antibody testing)

- Urine drug abuse test for screen, and the restriction assessments including alcohol breath test
- Twelve-lead ECG
- Vital signs (BP, HR, BT, and RR)
- Serum total IgE
- Hematology, clinical chemistry and urinalysis
- Adverse events, concomitant medications and restriction assessments
- Stool evaluation for ova and parasites only if indicated
- Serum pregnancy test in women of childbearing potential and follicle-stimulating hormone (FSH) test in female subjects whose last period was more than 1 year prior to the date of informed consent

6.1.2 Admission (Day -1) and Study Period (Day 1 to Day 127)

Subjects who successfully complete the screening visit will be domiciled in the study center as scheduled on Day -1. Inclusion and exclusion criteria will be reviewed to confirm subject eligibility on admission. If it is concluded that the subject is not eligible in Day -1 assessments, the subject will be considered as screening failure even if they passed the screening. Subject will enter the study center for the inpatient stay on Day -1. If the subject is eligible, he or she will be randomized on Day 1.

Meals will be served during the in-house stay. The in-house stay will provide an enhanced level of subject supervision and safety; it will also facilitate the maintenance of compliance and ensure that all study procedures are completed at the appropriate time intervals. The subjects can be discharged from the clinical unit on Day 4 after completion of the 72-hour assessments after study drug administration. The duration of in-house stay can be extended at the investigator's decision. After discharging, all study-related procedures and assessments will take place on an outpatient basis. The schedule of study assessments are specified in Table 11-1.

6.1.3 End-of-Study Visit (Day 127)

On Day 127 (±3 days), subjects will return to the clinical unit for an EOS visit. The following evaluations will be performed:

- Body weight
- Physical examination
- Hematology, clinical chemistry, and urinalysis
- Vital signs (BP, HR, BT, and RR)
- Twelve-lead ECG
- Urine pregnancy test in women of childbearing potential
- Pharmacokinetic and PD sampling

- Immunogenicity sampling
- Adverse events, concomitant medications and restriction assessments

If a subject withdraws prematurely after the study drug administration, the subject will be asked to return to the study site for the safety assessments of the EOS procedures. If deemed necessary by the investigator, then the subject will be asked to return at the regularly scheduled EOS visit.

6.2 Pharmacokinetic Assessments

Details of blood sampling time points and acceptable tolerance windows for PK assessments are described in Table 6-1. Blood will be processed and serum analyzed by a validated method for concentrations of CT-P39, EU-approved Xolair and US-licensed Xolair. Analysis of the samples will be performed at the central laboratory.

Table 6-1: Blood sampling time points for PK assessment

Day of study period	Time point	Window
Day 1	Pre-dose (prior to dosing on Day 1)	Pre-dose
	6 hours after start of administration	±15 minutes
	12 hours after start of administration	±15 minutes
Day 2	24 hours after start of administration	±15 minutes
Day 3	48 hours after start of administration	±1 hour
Day 4	72 hours after start of administration	±2 hours
Day 6	120 hours after start of administration	±8 hours
Day 8	168 hours after start of administration	
Day 11	240 hours after start of administration	
Day 15	336 hours after start of administration	
Day 22	504 hours after start of administration	
Day 29	672 hours after start of administration	±1 day
Day 43	1,008 hours after start of administration	
Day 57	1,344 hours after start of administration	
Day 71	1,680 hours after start of administration	±3 days
Day 85	2,016 hours after start of administration	
Day 106	2,520 hours after start of administration	
Day 127	3,024 hours after start of administration	

Abbreviation: PK = Pharmacokinetics.

6.3 Pharmacodynamics Assessments

Details of blood sampling time points and acceptable tolerance windows for PD assessments are described in Table 6-2. Free IgE and total IgE levels in the serum samples will be determined by validated immunoassays, separately.

Table 6-2: Blood sampling time points for PD assessment

Day of study period	Time point	Window
Screening[1]	Day -28 to Day -2	N/A
Day 1	Pre-dose (prior to dosing on Day 1)	Pre-dose
	6 hours after start of administration	±15 minutes
	12 hours after start of administration	±15 minutes
Day 2	24 hours after start of administration	±15 minutes
Day 3	48 hours after start of administration	±1 hour
Day 4	72 hours after start of administration	±2 hours
Day 6	120 hours after start of administration	±8 hours
Day 8	168 hours after start of administration	
Day 11	240 hours after start of administration	
Day 15	336 hours after start of administration	
Day 22	504 hours after start of administration	
Day 29	672 hours after start of administration	±1 day
Day 43	1,008 hours after start of administration	
Day 57	1,344 hours after start of administration	
Day 71	1,680 hours after start of administration	±3 days
Day 85	2,016 hours after start of administration	
Day 106	2,520 hours after start of administration	
Day 127	3,024 hours after start of administration	

Abbreviations: PD = Pharmacodynamics, IgE = Immunoglobulin E.

[1] At screening, blood sample for total immunoglobulin E (IgE) analysis will be collected at screening to confirm eligibility. Except for screening, blood samples for total IgE and free IgE analysis will be collected at the scheduled time points.

6.4 Immunogenicity Assessments

The potential immunogenicity of CT-P39, EU-approved Xolair and US-licensed Xolair will be assessed in samples collected at the time points specified in the table for immunogenicity assessments (Table 6-3). Unscheduled blood sampling will be performed when suspected immunogenicity related adverse event (e.g. hypersensitivity/allergic reactions) occurs.

The immunogenicity of CT-P39, EU-approved Xolair and US-licensed Xolair will be assessed at baseline and post-treatment serum measures by ADA and NAb in a validated immunoassay.

Table 6-3: Blood sampling time points for immunogenicity assessment

Day of study period	Time point	Window
Day 1	Pre-dose (prior to dosing on Day 1)	Pre-dose
Day 15	336 hours after start of administration	±8 hours
Day 43	1,008 hours after start of administration	±1 day
Day 85	2,016 hours after start of administration	±3 days
Day 127	3,024 hours after start of administration	±3 days

6.5 Safety Assessments

Safety will be assessed throughout the study by monitoring and recording of medical history, demographic and other baseline information, AEs, clinical laboratory assessments, and other safety assessments.

6.5.1 Medical History, Demographic and Other Baseline Information

The medical history (general medical history and medication history), demographic information (age, sex, ethnicity, race, height [cm]; without shoes, body weight [kg]; without shoes, and BMI [kg/m^2]), and other baseline characteristics (history of drug abuse, history of alcohol use, smoking history, history of caffeine use [or other stimulating beverages], special diet [e.g., vegetarian], history of blood or plasma/platelets donation or loss) will be recorded.

6.5.2 Adverse Events

6.5.2.1 Definitions of Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Subjects will be instructed to contact the investigator at any time after the ICF was signed if any symptoms develop.

A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in severity or frequency after exposure to study drug. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition; abnormal results of diagnostic procedures including laboratory test abnormalities are considered AEs if they fulfill the following:

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

- Are associated with clinical signs or symptoms judged by the investigator to have a clinically significant impact

Medical intervention such as surgery, diagnostic procedures, and therapeutic procedures are not AEs but the action taken to treat the medical condition. They should be recorded as treatment(s) of the AEs. The event term of primary cause should be recorded and reported instead of the term of surgery, diagnostic procedure, or therapeutic procedure.

6.5.2.1.1 Serious Adverse Events

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

6.5.2.1.2 Adverse Events of Special Interest

An AESI is an AE or occurrence that is designated to be of special interest and must be reported to CELLTRION, Inc. using the same reporting process as an AE.

The following events are considered events of clinical interest for this study:

- Allergic reactions Type I/anaphylaxis

  All AEs related to type I local or systemic allergic reactions including anaphylaxis and anaphylactic shock will be included. Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. Diagnosis of anaphylaxis will be based on the anaphylaxis criteria by National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (Sampson *et al*. 2006).

- Injection site reactions

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

- Serum sickness/serum sickness-like reactions (Type III hypersensitivity)

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

- Parasitic (helminth) infections

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

6.5.2.1.3 Suspected Unexpected Serious Adverse Events

A suspected unexpected SAE is defined as an event of which the nature or severity is not consistent with the applicable product information (e.g., IB) for an unapproved investigational product or the label (e.g., package insert, SmPC, or prescribing information), for an approved product. Assessment of expectedness will be made with the use of the IB and using the applicable reference documents. Therefore, if a treatment-related SAE occurs and it was not mentioned in the applicable product information, then it will be reported as a SUSAR.

6.5.2.2 Eliciting and Documenting Adverse Events

All AEs will be collected from the date the ICF is signed and AE reporting will continue until the end of the subject's participation in the study. All AEs will be followed until resolution or improvement to baseline, death, confirmed by the investigator that no further improvement could be expected, no more collection of clinical or safety data, or final database closure. Adverse events of special interest (e.g., allergic reactions Type I/anaphylaxis, injection site reactions, serum sickness/serum sickness-like reactions, and parasitic infections) will be closely monitored.

Subjects will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription medications and OTC).

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

6.5.2.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded in both the source documents and on the AE page of the eCRF. Information to be collected includes drug treatment, type of event, time of onset, action taken with study drug, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses,

reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states will also be reported.

Severity of adverse events will be graded base on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

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

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

The severity and the relationship or association of the study drug in causing or contributing to the AE will be characterized as defined in Sections 6.5.2.5 and 6.5.2.6, respectively.

Adverse events (and SAEs) should be reported until the EOS visit regardless of the relationship to the study drug. After the EOS visit, treatment-related SAE will be reported to CELLTRION, Inc. or its designee.

6.5.2.4 Reporting Serious Adverse Events

The investigator will review each SAE and evaluate the severity and the causal relationship of the event to study drug. All SAEs will be recorded from signing of informed consent until the EOS visit. Serious AEs occurring after the EOS visit and coming to the attention of the investigator must be reported only if there is (in the opinion of the investigator) reasonable causal relationship with the study drug.

Any SAE will be reported to the safety representative of CELLTRION Inc., [redacted] via e-mail (preferred) or fax using the SAE report form within 24 hours of awareness by the investigator, regardless of presumed causal relationship. The notification must be directed to:

[redacted]

[redacted]

If the subject is hospitalized during an SAE or because of an SAE, a copy of the hospital discharge summary will be e-mailed (or faxed) to [redacted]. Withdrawal of study treatment and all therapeutic measures will be at the discretion of the investigator or sub-investigator.

CELLTRION, Inc. or its designee is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with European Clinical Trials Directive (Directive 2001/20/EC), International Council for Harmonisation (ICH) guidelines, and/or local regulatory requirements.

CELLTRION, Inc. or its designee is responsible for reporting fatal or life-threatening SUSARs, (expedited reports) to the regulatory agencies and competent authorities within 7 calendar days after being notified of the event. CELLTRION, Inc. or its designee should report other SUSARs that are neither fatal nor life-threatening to the appropriate competent authorities (according to local guidelines), investigators, and central ethics committees by a written safety report within 15 calendar days of notification.

As a minimum requirement, the initial notification should provide the following information:

- Subject number
- Name of investigator and full study center address
- Serious adverse event term
- Name of study drug

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents if requested by sponsor or their designee (e.g., hospital records, discharge summaries, consultant reports, autopsy reports, etc.), with the study subject's personal identifiers removed. All relevant information obtained by the investigator through review of these documents will be recorded and e-mailed (or faxed) to the [redacted] within 24 hours of receipt of the information.

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

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

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or worsening of the pre-existing condition (e.g., for workup of persistent pre-treatment laboratory abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly physical examination);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery);

- Hospitalization for observation without a medical AE;
- Hospitalization purely for convenience (e.g., for easier performance of study assessments);
- Pre-planned treatments or surgical procedures; these should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

6.5.2.5 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the subject's daily activities. The severity of the AE will be graded based on the NCI CTCAE version 5.0, based on the following general guidelines (a semicolon indicates "or" within each description):

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[1].
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2].
Grade 4:	Life-threatening consequences; urgent intervention indicated.
Grade 5:	Death related to AE.

Abbreviations: ADL = Activities of daily living; AE = adverse event.
Source: NCI CTCAE version 5.0.
Note: a semicolon indicates "or" within each description.
[1] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[2] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. If an AE upgrades in severity or, changes from non-serious to serious, a new AE needs to be reported. If an AE downgrades in severity, it should not be reported as a new AE. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.5.2.6 Assessment of Causality

The investigator will assess the causality/relationship between the study drug and the AE and record that assessment results in the eCRF.

The most likely cause of an AE will be indicated in the eCRF with details of the concomitant disease or medication or other cause.

The causal relationship of the AE to study drug will be described using following classification:

- Definite:

  This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (e.g., concurrent illness, progression of disease state, concurrent medication reaction, etc.) do not appear to explain the event.

- Probable:

  This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely.

- Possible:

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

- Unrelated:

  This relationship suggests that there is no association between the study drug and the reported event.

6.5.2.7 Procedure for Notification of Serious Adverse Event and Suspected Unexpected Serious Adverse Reactions to Human Research Ethics Committee

If required by applicable local regulations, the investigator shall promptly notify the relevant Human Research Ethics Committee (HREC) (in addition to CELLTRION, Inc.) of any SAE (including follow-up information of SAEs) and SUSARs that occurred at his/her site or brought to his/her attention by CELLTRION, Inc. The investigator shall verify that the HREC acknowledges receipt of the information.

6.5.3 Clinical Laboratory Assessments

The safety laboratory analyses of blood including hematology, and clinical chemistry, as well as urine drug screen will be performed according to validated methods and procedures. Laboratory analyses will be performed by the local laboratories.

The following laboratory variables will be determined in accordance with the Schedule of Assessments (Table 11-1):

- **Hematology**: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, and platelet count.
- **Clinical chemistry**: total protein, sodium, potassium, calcium, chloride, magnesium, phosphate, albumin, glucose, total cholesterol, triglycerides, C-reactive protein, urea, creatinine, uric acid, bilirubin (total, direct), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, lactate dehydrogenase, creatine phosphokinase, and troponin I.
- **Serology**: HBsAg, anti-HCV, HIV testing

- **Urinalysis**: pH, specific gravity, glucose, ketones, nitrite, protein, bilirubin, urobilinogen, occult blood, and microscopic examination.
- **Urine drug, alcohol, and nicotine:** The screen for drugs of abuse including the following: amphetamine class (amphetamines, methamphetamines, methylenedioxymethamphetamines, etc.), methadone, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol. The urine test for drugs of abuse will be performed at screening and Day -1 (The urine test can be repeated once at the discretion of investigator). An alcohol breath test will also be performed at screening and Day -1. The history of drug abuse, alcohol, and nicotine use will be taken by the investigator at screening and Day -1.
- **C3, C4 and total hemolytic complement assessment:** Complement (C3 and C4) and total hemolytic complement will be assessed on Day -1 to establish the baseline value. Additional clinical laboratory test samples will be collected and C3, C4, and total hemolytic complement will be assessed in the case of Type III hypersensitivity. Total hemolytic complement will be assessed by CH_{50} assay.

Any value outside the normal range will be flagged for the attention of the investigator or designee at the site. The investigator or designee will indicate whether or not the value is of clinical significance. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (e.g., active observation, diagnostic measures, or therapeutic measures).

If the result of any test (or repeated test, if done) from the samples taken during the screening period is indicated as clinically significant, the study subject will NOT be allowed into the study without permission of the Sponsor/Medical Monitor. However, retest is permitted only once during screening period based on the investigator's judgment. Additional testing during the study period may be done if medically indicated. If a clinically significant abnormality is found in the samples taken after dosing, during the study, and/or at the EOS visit, it should be recorded as an AE and the study subject will be followed until the test(s) has (have) normalized or stabilized or final database closure.

6.5.4 Other Safety Assessments

6.5.4.1 Injection Site Reaction

Injection site reactions will be assessed 30 minutes (±10 minutes) after study drug administration, as specified in the Schedule of Assessments (Table 11-1).

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

6.5.4.2 Local Site Pain Assessment

Local site pain will be assessed using 100 mm VAS immediately (within 15 minutes) after study drug administration (Day 1) according to the Schedule of Assessments (Table 11-1). Subjects will be asked to indicate their current level of pain intensity by drawing a single vertical line (|) on the 100 mm line (Section 11.2).

6.5.4.3 Hypersensitivity Assessment/Allergic Reactions Monitoring

For hypersensitivity monitoring, vital signs and either 3-lead or 12-lead ECG will be done. Assessment time points and acceptable tolerance windows for hypersensitivity monitoring are described in Table 6-4.

Table 6-4: Schedule of Assessment for Hypersensitivity Monitoring

Assessment	Day of study period	Time points	Window
Vital sign	Day 1	Pre-dose (prior to dosing on Day 1)	Pre-dose (within 30 minutes)
		30 minutes after administration	±10 minutes
		1 hour after administration	
		2 hours after administration	
		6 hours after administration	±1 hour
		12 hours after administration	±1 hour
3-lead/12-lead ECG	Day 1	Pre-dose (prior to dosing on day 1)	Pre-dose (within 30 minutes)
		2 hours after administration	±30 minutes

Abbreviation: ECG = Electrocardiogram.

In addition, hypersensitivity/allergic reactions will be monitored by routine continuous clinical monitoring. In case of hypersensitivity, emergency medication and equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation will be available and an ECG can be performed. Subjects who develop a life-threatening hypersensitivity/allergic reaction must be withdrawn from study.

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

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

- Immunogenicity
- Clinical laboratory analyses
- Complement (C3 and C4) and total hemolytic complement

6.5.4.4 Vital Signs, Weight, and Height

Vital signs will be assessed at time points specified in the Schedule of Assessments (Table 11-1). The following vital signs will be measured:

- Blood pressure (systolic and diastolic [mmHg]);

- Heart rate (beats per minute);
- Body temperature (℃);
- Respiratory rate (breaths per minute).

Blood pressure, HR, RR and BT recordings will be made after the study subject has been resting for at least 5 minutes. Body weight will be measured according to the Schedule of Assessments (Table 11-1).

Vital sign measurements will also be performed before and after study drug administration as part of the hypersensitivity monitoring (Section 6.5.4.3).

6.5.4.5 Electrocardiogram

The 12-lead ECG tests will be obtained after the subject has been rested for at least 5 minutes and will be performed at the time points specified in the Schedule of Assessments (Table 11-1).

Twelve-lead or 3-lead ECG for hypersensitivity monitoring will also be performed according to Table 6-4. Additional ECGs may be performed if the subject experiences cardiac symptoms or cardiac lab abnormality is reported.

If, following ECG review by the investigator, there are any ECG findings that would indicate cardiac insufficiency or QT prolongation, the subject will be referred to a cardiologist to confirm the abnormality and the event will be recorded in the source documents and the eCRF. Regardless of the ECG result, further consultation and evaluation by a cardiologist may be performed at the discretion of the investigator.

6.5.4.6 Physical Examination

Physical examinations will be performed at time points specified in the Schedule of Assessments (Table 11-1).

The physical examination includes an assessment of general appearance and a review of systems. Information about the physical examination will be recorded by the investigator, or delegated clinical staff member, in both the source documents and the eCRF. Any abnormalities will be recorded in the source documents. Clinically significant findings and illnesses reported after the start of the study that meet the definition of an AE will be recorded as such in the source documents and eCRF.

6.5.4.7 Pregnancy Test

A serum pregnancy test will be performed at screening, and urine pregnancy test will be performed on women of childbearing potential on Day -1 and EOS visit, as indicated in the Schedule of Assessments (Table 11-1). A FSH test will be performed on female subjects whose last period was more than 1 year prior to the date of informed consent, to confirm postmenopausal status at screening. A female subject whose last period was more than 1 year prior to the date of informed consent and serum FSH level is ≥40 IU/L will be considered postmenopausal. Throughout the

study, a urine pregnancy test will be performed when there is any possibility of pregnancy, and a confirmatory serum pregnancy test will be performed if a urine pregnancy test result is positive.

If a female subject or the partner of a male subject becomes pregnant during the study, the pregnancy must be reported to safety representative of CELLTRION, Inc., [redacted] (contact details included in Section 6.5.2.4) within 24 hours of the study site's knowledge of the pregnancy while confirmation is pending. Once the pregnancy is confirmed with a serum pregnancy test for female subjects, the subjects will be withdrawn from the study. The study site must complete the supplied pregnancy form (female subject or female partner of a male subject) and return it to [redacted] within 24 hours after acquisition of the consent for the pregnancy form. If a withdrawn female subject or the female partner of withdrawn male subject becomes pregnant within 3 months after the study drug administration, the pregnancy must also be reported as above. The outcome of all pregnancies must be followed and documented even if the subject was withdrawn from the study. Spontaneous miscarriage, stillbirth/neonatal death and congenital abnormalities/birth defects will be reported as SAEs.

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

6.6 Sample Collection, Labelling, Storage and Shipment

6.6.1 Sample Collections

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

6.6.1.1 Pharmacokinetic Sampling

Blood will be collected per blood sampling time points for PK assessment sample at the time points specified in the Schedule of PK Assessments (Table 6-1). All samples will be collected as close as possible to the scheduled time point and the actual sampling time will be recorded. If samples are not physically able to be collected within the specified time window, they should be collected at the earliest time possible outside of the window. An explanation will be provided in the eCRF for any missed or mishandled samples and for samples collected outside the specified time windows.

The samples will be split into separate containers or tubes, and processed, stored, and shipped under the appropriate conditions as outlined in a separate laboratory manual.

6.6.1.2 Pharmacodynamic Sampling

Blood samples for free IgE and total IgE will be obtained at the time points specified in the Schedule of PD assessments (Table 6-2).

6.6.1.3 Clinical Laboratory Testing

Blood samples for clinical laboratory testing will be collected for analysis throughout the study at the time points specified in the Schedule of Assessments (Table 11-1).

An additional blood sample for serology test (HbsAg, anti-HCV, and HIV antibody test) will also be required at screening. A serum pregnancy test sample will be required at screening visit for women of childbearing potential who have not been surgically sterilized.

6.6.1.4 Immunogenicity Sampling

Blood samples for immunogenicity assessments will be obtained at the time points specified in the table of immunogenicity assessments (Table 6-3). The samples will be split into separate containers or tubes, and processed, stored, and shipped under the appropriate conditions as outlined in a separate laboratory manual. If the blood sample was unable to be analyzed or was missing, some blood samples collected for PK assessment at the same time point could be used for immunogenicity assessment. Analysis of the samples will be performed at the central laboratory.

For immunogenicity assessment, in addition to the pre-specified sampling schedule, unscheduled blood sampling will be performed when suspected immunogenicity related adverse event (e.g. hypersensitivity/allergic reactions) occurs in order to establish the clinical relevance of ADAs as specified in the FDA Guidance for industry entitled “Immunogenicity Assessment for Therapeutic Protein Products (FDA 2014)”.

6.6.2 Sample Labeling

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

6.6.3 Sample Storage and Shipment

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

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

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

7. STATISTICAL METHODS

Statistical analyses will be performed using [redacted].

The statistical methods for this study will be described and detailed in statistical analysis plan (SAP), which will be finalized prior to locking of the database.

Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the final study report.

7.1 General Considerations

Continuous data will be summarized by treatment group using descriptive statistics (number, mean, standard deviation [SD], minimum, median and maximum), and categorical data will be summarized by treatment group using frequency tables (number and percentage), unless otherwise specified.

Any outliers that are detected during the blind review of the data will be investigated. Methods for dealing with outliers will be defined in the SAP, prior to unblinding.

7.2 Study Population

7.2.1 Disposition of Subjects

The number and percentage of subjects entering and completing the clinical study will be presented by treatment.

7.2.2 Protocol Deviations

Deviations from the protocol, including deviations of inclusion/exclusion criteria will be defined as “minor” or “major” before database lock.

7.2.3 Analysis Sets

Intent-to-treat (ITT) Set: The ITT Set is defined as all subjects enrolled and randomly assigned to receive a dose of the study drugs (CT-P39, EU-approved Xolair, or US-licensed Xolair), regardless of whether or not any study drug was administered. Subjects will be assigned to treatment groups based on randomization.

Safety Set: The Safety Set is defined as all randomly assigned subjects who receive a full or partial dose of study drug (CT-P39, EU-approved Xolair, or US-licensed Xolair). Subjects will be assigned to treatment groups based on treatment actually received.

Pharmacokinetic (PK) Set: The PK Set is defined as all subjects who receive a complete dose of study drug (CT-P39, EU-approved Xolair, or US-licensed Xolair) and who have at least one post-treatment PK result with a concentration above the lower limit of quantification for omalizumab. Subjects will be analyzed according to the treatment they actually received. If any subject is found to be non-compliant with respect to dosing, a determination of the PK Set will be made on a case-by-case basis at the blinded Data Review Meeting before unblinding.

Pharmacodynamic (PD) Set: The PD Set is defined as all subjects who receive a complete dose of study drug (CT-P39, EU-approved Xolair, or US-licensed Xolair) and who have at least one post-treatment PD result. Subjects will be analyzed according to the treatment they actually received.

The secondary endpoints will be analyzed for Part 1 and Part 2, separately. To report the initial safety, PK, PD and immunogenicity results, data up to Day 29 will be analyzed in Part 1. The detailed methods about statistical analysis will be described in a SAP.

7.3 Pharmacokinetic Analyses

Pharmacokinetic analysis will be performed on the PK Set. Statistical analyses will be carried out independently for each part and the primary PK endpoints will be analyzed only for Part 2 subjects. The secondary PK endpoints will be analyzed in all subjects (both Part 1 and Part 2).

Pharmacokinetic concentration data and parameters will be listed by subject including actual sampling times relative to dosing. Serum concentrations and parameters will be summarized by treatment group. The following descriptive statistics will be presented for serum concentrations and parameters: number of subjects, mean, SD, coefficient of variation (CV), geometric mean, median, minimum and maximum values.

The non-compartmental PK parameters listed in Sections 3.2.1 and 3.2.2 will be calculated using [redacted], based on the following guidelines:

- C_{max} will be obtained directly from the concentration-time data
- T_{max} is the time at which C_{max} is observed
- λ_z will be estimated at terminal phase by linear regression after log-transformation of the concentrations:
  - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression
  - A minimum number of 3 data points in the terminal phase will be used in calculating λ_z with the line of regression starting at any post-C_{max} data point (C_{max} will not be part of the

regression slope). The adjusted coefficient of determination (R^2 adjusted) in general should be greater than 0.85. All the derived parameters (e.g., λ_z, $t_{½}$, $AUC_{0\text{-inf}}$, CL/F, V_z/F and $\%AUC_{ext}$) will need to be flagged accordingly

  - An appropriate number of decimal places will be used for λ_z to enable the reported value of $t_{½}$ to be calculated

- $t_{½}$ will be calculated as $\ln 2/\lambda_z$
- $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ will be calculated as follows:
  - The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations
- CL/F will be calculated as dose/$AUC_{0\text{-inf}}$
- V_z/F will be calculated as CL/λ_z
- $\%AUC_{ext}$ will be calculated as $(1 - [AUC_{0\text{-last}}/AUC_{0\text{-inf}}]) \times 100$. The $\%AUC_{ext}$ should not exceed 20% for each individual profile. If the $\%AUC_{ext}$ is more than 20%, the individual result should be flagged as well as all parameters depending on $AUC_{0\text{-inf}}$. All the derived parameters (i.e., $AUC_{0\text{-inf}}$, V_d and CL/F) will need to be flagged accordingly.

The statistical analysis of the log-transformed primary endpoints ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}) will be based on an analysis of covariance model with treatment as a fixed effect and body weight, total IgE level, and sex as covariates. The final confirmation of covariates and details will be described in the SAP. The similarity of PK between CT-P39 *versus* EU-approved Xolair, CT-P39 *versus* US-licensed Xolair, and EU-approved Xolair *versus* US-licensed Xolair will be concluded if the 90% CIs of the ratios of geometric means of each comparison are entirely contained within 80% to 125% for $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}. Back transformation will provide the ratio of geometric means and 90% CIs for these ratios.

Secondary endpoints ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max} for Part 1 and T_{max}, $t_{½}$, $\%AUC_{ext}$, λ_z, CL/F, and V_z/F for both parts) will be independently analyzed for each part.

Graphical presentations of PK data and additional PK parameters may be added at the discretion of the PK scientist, as appropriate.

7.4 Pharmacodynamic Analyses

Pharmacodynamic analysis will be performed on the PD Set.

Serum concentration data of free IgE and total IgE and parameters will be listed by subject including actual sampling times relative to dosing. Serum concentrations and parameters will be summarized by treatment group. The following descriptive statistics will be presented for serum concentrations and parameters: number of subjects, mean, SD, CV, geometric mean, median, minimum and maximum values.

For free IgE, following parameters will be calculated:

- Minimum serum concentration (C_{min})
- Time to C_{min} (T_{min})
- Maximum percentage decrease in serum free IgE concentration from screening (max % decrease)

For total IgE, following parameters will be calculated:

- C_{max}
- T_{max}
- Maximum percentage increase in serum total IgE concentration from screening (max % increase)

Graphical presentations of PD data and additional PD parameters may be added, as appropriate.

7.5 Immunogenicity Analyses

Immunogenicity analyses will be conducted on the Safety Set. The number and percentage of subjects with ADA and NAb results will be presented by treatment group and visit.

7.6 Safety Analyses

All safety analyses will be conducted on the Safety Set.

7.6.1 Demographic, Baseline, and Background Characteristics

Demographics (including age, gender, ethnicity and race) and baseline and background characteristics will be presented in summary tables by treatment group in ITT Set. Qualitative data (e.g., medical history) will be summarized in contingency tables, and quantitative data (e.g., age) will be summarized using quantitative descriptive statistics.

7.6.2 Adverse Events

Severity of AEs will be graded based on the NCI CTCAE version 5.0 and will be coded to system organ class (SOC) and preferred term (PT) according to MedDRA. All safety data will be listed and summarized by treatment group as appropriate. All safety data will be analyzed descriptively.

The following TEAE summaries will be reported by SOC, PT, relationship, intensity, and treatment group:

- The number and percentage of subjects reporting at least 1 TEAE;
- The number and percentage of subjects reporting at least 1 treatment-emergent serious adverse event;
- The number and percentage of subjects leading to permanent discontinuation due to an TEAE;
- The number and percentage of subjects with AESI.

At each level of summarization for the number of subjects with an event, a subject is counted only once if they reported one or more events and only the worst intensity will be counted at each level of summarization.

7.6.3 Clinical Laboratory Tests

Clinical laboratory tests will be summarized by treatment group at each scheduled collection time. For continuous parameters, change from baseline will also be summarized for all post injection scheduled collection times. All laboratory results will be listed. Shift tables will be generated for categorical clinical laboratory test results using low/normal/high or normal/abnormal classification, as appropriate.

7.6.4 Vital Signs

Vital signs will be listed and summarized, by treatment group at each scheduled collection time. Change from baseline will also be summarized for all post injection scheduled collection times.

7.6.5 Electrocardiogram

Overall assessment and ECG parameters will be listed by treatment group and visit. In addition, overall assessment in ECG will be summarized by treatment group in a shift table.

7.6.6 Physical Examination

A shift table comparing the categorical results at scheduled post baseline visit with those at baseline will be summarized by treatment group and visit. All physical examination findings will be presented in a data listing.

7.6.7 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. All prior and concomitant medications data will be listed and summarized by treatment group as appropriate. These medications will be summarized by drug class and PT.

7.7 Interim Analyses

No formal interim analyses will be performed in this study.

7.8 Determination of Sample Size

Overall, a total of approximately 177 subjects will be enrolled in this study.

For Part 1, approximately 30 healthy subjects will be randomized to receive either CT-P39 or EU-approved Xolair. A sample size justification based on a formal statistical hypothesis is not relevant for Part 1, hence a formal statistical inference will not be made.

For Part 2, 126 subjects (42 in each arm) with evaluable data in the primary PK Set provide 90% statistical power to show that the 90% confidence interval (CI) for the ratio of geometric means of PK parameters (CT-P39 to EU-approved Xolair, CT-P39 to US-licensed Xolair, and EU-approved Xolair to US-licensed Xolair) lies within equivalence margins of 80% to 125%

assuming that the CV is 30% and the expected ratio is 1.03. The sample size is calculated from two one-sided tests with each at 5% significance level. Accounting for 15% of randomized subjects excluded from the PK Set, approximately 147 subjects (49 in each group) will be randomized to achieve the required sample size of 42 per group.

8. STUDY MANGEMENT

8.1 Analytical Facilities

Any analytical facilities and procedures utilized for this study must be Good Laboratory Practice and Good Clinical Practice (GCP) compliant. The following analytical facility will be used:

Laboratory for Pharmacokinetic, Pharmacodynamic (free IgE), and Immunogenicity Testing

[redacted]

Laboratories for Pharmacodynamic Testing (total IgE)

[redacted]

8.2 Monitoring

8.2.1 Data and Safety Monitoring Board

An independent data and safety monitoring board will not be used for this study.

8.2.2 Monitoring of the Study

The clinical monitor, as a representative of CELLTRION, Inc., is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study center at periodic intervals in addition to maintaining necessary telephone and e-mail contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

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

8.2.3 Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, HREC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, their representatives, or regulatory agency access to all study records.

The investigator will promptly notify CELLTRION, Inc. and study center(s) of any audits scheduled by any regulatory authorities.

8.3 Management

8.3.1 Modification of Protocol

Before the start of the clinical study, the clinical study protocol and other relevant documents will be approved by the HREC, in accordance with local legal requirements. CELLTRION, Inc. must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the clinical study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, which must be released by the responsible staff, and receive HREC approval prior to implementation (as appropriate).

Administrative changes may be made without the need for a formal amendment but will also be mentioned in the integrated clinical study report (CSR). All amendments will be distributed to all study protocol recipients, with appropriate instructions.

8.3.2 Protocol Deviations

The investigator or designee will document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or change to, the protocol to eliminate an immediate hazard to study subjects without prior HREC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments will be submitted to the HREC for review and approval, to CELLTRION, Inc. for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by CELLTRION, Inc. and the HREC and agreed to by the investigator. A significant deviation occurs when there is non-adherence to the protocol by the subject or investigator that results in a significant and additional risk to the subject's rights, safety and well-being. Significant deviations can include non-adherence to inclusion or exclusion criteria, or non-adherence to a regulatory agency's regulations or ICH GCP guidelines, and will lead to the subject being withdrawn from the study (Section 4.4).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of deviations. The HREC will be notified of all protocol deviations, if appropriate, in a timely manner.

8.4 Premature Termination of the Clinical Trial

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

If the study is terminated prematurely by CELLTRION, Inc., all subjects will be kept fully informed and an appropriate follow-up examination of the subjects will be arranged. The investigator will inform the HREC of any premature termination or suspension of the study, where applicable.

Should the study be terminated and/or the site closed for whatever reason, study related documents should be archived at the site according to Section 9.5. Used/unused study drug should be managed according to Section 5.1.3. Any actions of the investigator required for assessing or maintaining study subject safety will continue as required, despite termination of the study by CELLTRION, Inc.

8.5 Clinical Study Report

CELLTRION, Inc. plans to prepare two CSRs.

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

CELLTRION, Inc. plans to prepare two CSRs to report the followings:

- Data for subjects in Part 1 up to Day 29
- All data for all subjects in both parts after completion of the study

To report the initial safety, PK, PD, and immunogenicity results, data up to Day 29 will be analyzed in Part 1. Plans for code break for this first analysis and maintaining blindness are specified in Section 5.5.

9. DATA COLLECTION AND QUALITY ASSURANCE

9.1 Data Quality Assurance

CELLTRION, Inc. or designee will conduct a study initiation visit to verify the qualifications of the investigator, inspect the facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical site and CELLTRION, Inc. is essential to ensure that the safety of the study is monitored adequately. The investigator will make all appropriate safety assessments on an ongoing basis. All information recorded in the eCRF for this clinical study must be consistent with the subject's source documentation. The Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to GCP for compliance with applicable government regulations (ICH E6(R2) 2016). The Study Monitor will be an authorized individual designated by CELLTRION, Inc. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the investigator.

9.2 Data Collection

Electronic Data Capture (EDC) will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study site. Data collection will be completed by authorized study site staff delegated by the investigator. Appropriate training and security measures will be completed with the investigator and all authorized study site staff prior to the study being initiated and any data being entered into the system for any study subjects. The investigator will ensure that the data collected are accurate, complete and legible.

The responsible study monitor will check data at the monitoring visits to the clinical study site. Data will be monitored within the eCRF by the study monitor before being exported. Any changes made during monitoring will be documented with a full audit trail within the eCRF.

All clinical work conducted under this protocol is subject to GCP regulations.

9.3 Case Report Forms and Source Documents

All data obtained during the clinical study will be promptly recorded in the eCRF. All source documents from which eCRF entries are derived will be placed in the subject's personal records.

The original eCRF entries for each subject will be checked against source documents by the monitor. Instances of missing or uninterpretable data will be discussed with the investigator for resolution.

9.4 Data Management

Data management of all data documented will be performed under the responsibility of CRO or CELLTRION, Inc.

A Data Management Plan (DMP) will be provided to CELLTRION, Inc. describing the work and data flow within this clinical study which will be using an EDC System. The EDC System will be customized for this study. Both the EDC System and DMP will be sent to CELLTRION, Inc. for review and approval. The DMP must be finalized before database lock.

For the EDC, a database structure that will host this study will be created and an interface to access it will be implemented. The system will establish and maintain the use of the computerized system according to the relevant SOP. Practical training sessions will be conducted on site to system users to teach them how to use the system.

Data will be collected individually in eCRFs. After all study materials are delivered and the eCRF is completed and validated, data will be entered in the clinical data storage system. Data will be available immediately to the data manager after it has been entered and therefore the data verification and validation process can start earlier contributing to data quality.

Any missing, implausible, or inconsistent recordings will be referred back to the investigator using a data query form and will be documented for each individual subject before clean file is declared.

The AEs will subsequently be coded using the MedDRA, and prior and concomitant medications will be coded using the World Health Organization Drug Dictionary.

9.5 Archiving Study Documents

According to ICH guidelines, essential documents will be retained until at least 15 years after the date on which the results of the study are submitted to the regulatory authorities in support of an allocation for a research or marketing permit, or completion date for study by approval or disapproval of any application, whichever is later. These documents will be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with CELLTRION, Inc. It is CELLTRION, Inc.’s responsibility to inform the investigator/institution as to when these documents no longer need to be retained.

10. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

10.1 Good Clinical Practice

The procedures set out in this clinical study protocol are designed to ensure that CELLTRION, Inc. and the investigator abide by the principles of the ICH guidelines on GCP and the Declaration of Helsinki (WMA 2013). The clinical study also will be carried out in keeping with national and local legal requirements.

10.2 Informed Consent

Before each subject is enrolled in the clinical study, written informed consent will be obtained from the subject according to the regulatory and legal requirements of the participating country and will be retained as part of the clinical study records. The investigator will not undertake any investigation specifically required only for the clinical study until written consent has been obtained. The terms of the consent and signed date must also be documented in the eCRF.

The investigator must ensure that the subject received full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified that they are free to withdraw from the study at any time without prejudice to future care. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the responsible HREC and signed by all subjects subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

10.3 Confidentiality Data Protection

All clinical study findings and documents will be regarded as confidential. Study documents (protocols, IB, and other materials) will be stored appropriately to ensure their confidentiality. The investigator and members of his/her research team (including the HREC) must not disclose such information without prior written approval from CELLTRION, Inc., except to the extent necessary to obtain informed consent from subjects who wish to participate in the study or to comply with regulatory requirements.

The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number. Documents that identify the subject (e.g., the signed ICF) must be maintained in confidence by the investigator.

10.4 Liability and Insurance

CELLTRION, Inc. will take out reasonable third party liability insurance cover in accordance with all local legal requirements. The civil liability of the investigator; the persons instructed by him/her and the hospital, practice, or institute in which they are employed; and the liability of the CELLTRION, Inc. with respect to financial loss due to personal injury and other damage that may

arise as a result of the carrying out of this study are governed by the applicable laws and GCP guidelines.

CELLTRION, Inc. will arrange for subjects participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

The method and manner of compensation to subjects should comply with applicable regulatory requirement(s).

10.5 Publication Policy

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

All data are the property of CELLTRION, Inc. and cannot be published without its prior authorization, but data and any publication thereof will not be unduly withheld.

11. APPENDICES

11.1 Appendix 1: Schedule of Assessments

Table 11-1: Schedule of Assessments

Assessments	Screening	In-House Stay					Outpatient Visit											EOS
Day of Study Period	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**6**	**8**	**11**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**106**	**127**
Visit Window (Day)												**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**
Informed consent	X																	
Demographics	X																	
Medical history	X	X																
Inclusion and exclusion criteria	X	X																
Body weight & height[1]	X	X																X
Drugs of abuse/alcohol and nicotine check[2]	X	X																
Serum pregnancy test[3]	X																	
Urine pregnancy test[3]		X																X
FSH test[4]	X																	
Stool and parasite evaluation[5]	X																	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology, clinical chemistry, and urinalysis[7]	X	X			X			X		X		X		X		X		X
Serology[8]	X																	
Physical examination[9]	X	X			X													X
12-lead electrocardiogram	X				X			X				X		X		X		X
Randomization			X[6]															
Study drug administration			X															
Hypersensitivity/allergic reactions and injection site reaction monitoring			X[10]															
C3, C4, and total hemolytic complement[11]		X	(X)															
Local site pain by VAS[12]			X															
Serum total IgE sampling[13]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum free IgE sampling[14]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Assessments	Screening	In-House Stay					Outpatient Visit											EOS
Day of Study Period	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**6**	**8**	**11**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**106**	**127**
Visit Window (Day)												**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**
PK sampling [15]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity sampling[16]			X[6]							X			X			X		X
Restriction assessments	X																	
Prior and/or concomitant medications[17]	X																	
Adverse event monitoring	X																	

Abbreviations: ECG = electrocardiogram; EOS = end-of-study; FSH = follicle-stimulating hormone; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; PD = pharmacodynamics; PK = pharmacokinetic; ULN = upper limit of normal; VAS = visual analog scale.

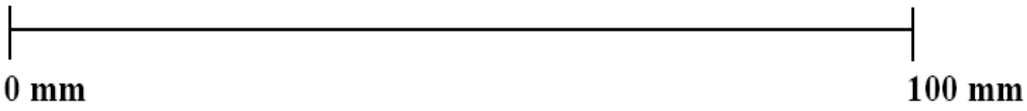
1. Height will be measured at screening only.
2. Drug abuse testing includes the following: amphetamine class (amphetamines, methamphetamines, methylenedioxymethamphetamines, etc.), methadone, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol. The urine test for drugs of abuse will be performed at screening and Day -1 (The urine test can be repeated once at the discretion of investigator). An alcohol breath test will also be performed at screening and Day -1. The history of drug abuse, alcohol and nicotine use will be taken by the investigator at screening and Day -1.
3. A serum pregnancy test on women of childbearing potential will be performed at screening visit. A urine pregnancy test will be performed in women of childbearing potential on Day -1 and end-of-study (EOS) visit. Throughout the study, a urine pregnancy test will be performed when there is any possibility of pregnancy, and a confirmatory serum pregnancy test will be performed if a urine pregnancy test result is positive.
4. A follicle-stimulating hormone (FSH) test will be performed on female subjects whose last period was more than 1 year prior to the date of informed consent, to confirm postmenopausal status at screening. A female subject whose last period was more than 1 year prior to the date of informed consent and serum FSH level is ≥40 IU/L will be considered postmenopausal.
5. Stool ova and parasite examination will be performed in subjects with an absolute eosinophil count >2 x ULN AND risk factors for parasitic disease listed at the exclusion criterion 5).
6. Pre-dose on Day 1.
7. The following laboratory variables will be determined: **hematology** (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and platelet count), **clinical chemistry** (total protein, sodium, potassium, calcium, chloride, magnesium, phosphate, albumin, glucose, total cholesterol, triglycerides, C-reactive protein, urea, creatinine, uric acid, bilirubin [total, direct], alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, lactate dehydrogenase, creatine phosphokinase, and troponin I), and **urinalysis** (pH, specific gravity, glucose, ketones, nitrite, protein, bilirubin, urobilinogen, occult blood, and microscopic examination).
8. Serology tests will be performed at the screening visit for HbsAg, anti-HCV, HIV testing.
9. Physical examination will be done at screening, on Day -1, 3 and at EOS.
10. For hypersensitivity monitoring, vital sign measurements will be performed before the start of the study drug administration (pre-dose) and at 30 minutes, 1, 2, 6, and 12 hours after start of administration on Day 1. Electrocardiogram (ECG) will be performed before the start of the study drug administration (pre-dose) and at 2 hours after start of administration on Day 1. Assessment time points and acceptable tolerance windows for hypersensitivity monitoring are described in Table 6-4. Either 3-lead or 12-lead ECG can be used for hypersensitivity monitoring. Additional ECG will be performed if a subject experiences cardiac symptoms. In addition, hypersensitivity/allergic reactions will

be monitored by routine continuous clinical monitoring. If the subject experiences any of hypersensitivity signs and symptoms after discharge, the subject can visit the study center for further assessments. The diagnostic assessment such as serum samples for C3, C4, and total hemolytic complement can be ordered to determine serum sickness based on the investigator's discretion. Injection site examination including but not limited to evaluating erythema, pain, bruising, bleeding, and other signs of discomfort or skin reaction to be completed at least 30 minutes after injection. In the event of significant skin reactions, appropriate informal photographs may be taken. Skin biopsy may also be considered.

11. Complement (C3 and C4) and total hemolytic complement will be assessed on Day -1 to establish the baseline value. Additional serum samples for complement (C3 and C4) and total hemolytic complement will be assessed in the case of Type III hypersensitivity.
12. Local site pain will be observed immediately (within 15 minutes) after the study drug administration on Day 1.
13. Serum total IgE sample will be collected at screening to confirm eligibility. Total IgE samples for PD analysis will be collected on Day 1 before dosing, at 6, 12, 24 (Day 2), 48 (Day 3) and 72 hours (Day 4) from the start of administration and on Days 6, 8, 11, 15, 22, 29, 43, 57, 71, 85, 106 and 127 (EOS). Details of blood sampling time points and acceptable tolerance windows for PD assessments are described in Table 6-2.
14. Free IgE samples for PD analysis will be collected on Day 1 before dosing, at 6, 12, 24 (Day 2), 48 (Day 3) and 72 hours (Day 4) from the start of administration and on Days 6, 8, 11, 15, 22, 29, 43, 57, 71, 85, 106 and 127 (EOS). Details of blood sampling time points and acceptable tolerance windows for PD assessments are described in Table 6-2. Analysis will be performed at the central laboratory.
15. Blood samples for PK analysis will be collected on Day 1 before dosing, at 6, 12, 24 (Day 2), 48 (Day 3) and 72 hours (Day 4) from the start of administration and on Days 6, 8, 11, 15, 22, 29, 43, 57, 71, 85, 106 and 127 (EOS). Details of blood sampling time points and acceptable tolerance windows for PK assessments are described in Table 6-1. Analysis will be performed at the central laboratory.
16. Unscheduled blood sampling will be performed when suspected immunogenicity related adverse event (e.g. hypersensitivity/allergic reactions) occurs. Analysis will be performed at the central laboratory.
17. Prior and/or concomitant medication use will be recorded for the 30 days before the signed date of informed consent form (ICF) until the EOS visit (inclusive of the applicable periods for prohibited medications as defined in Section 4.3).

11.2 Appendix 2: Visual Analogue Scale Subject's Assessment of Pain

Subject assessment of local site pain is measured by the subject indicating the extent of their pain by marking one line (|) through the 100 mm line (0 mm equals no pain and 100 mm equals most severe pain). The length of the line is measured from the left (in mm) and the value (in mm) recorded in the subject's eCRF.



No pain Most severe pain

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