21 March 2024
EMA/153515/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Omlyclo

International non-proprietary name: omalizumab

Procedure No. EMEA/H/C/005958/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

ACE	Affinity capture elution
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism and excretion
AE	Adverse event
AESI	Adverse event of special interest
AET	Analytical evaluation threshold
ANCOVA	Analysis of covariance
APG	Acidic peak group
AS	Active substance
AUC	Area under the concentration-time curve
BMI	Body max index
BPG	Basic peak group
CCI	container closure integrity
CD	Circular dichroism
CE-SDS	Capillary electrophoresis sodium dodecyl sulfate
CFU	Colony forming unit
CI	Confidence interval
cIEF	Capillary isoelectric focussing
CIPT	Critical in process tests
CLT	Celltrion plant
Cmax	Maximum serum concentration
CMC	Chemistry, manufacturing and control
COVID-19	Coronavirus disease of 2019
CPP	Critical process parameter
CRO	Clinical research organization
CSR	Clinical study report
Ctrough	Trough serum concentration
CQA	Critical quality attributes
DNA	Deoxyribonucleic acid
DP	Drug product
DS	Drug substance
DSC	Differential scanning calorimetry
DSMB	Data safety monitoring board
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ELISA	Enzyme-linked immunosorbent assay
EOS	End-of-study
EPCB	End of production cell bank
EU	European Union
FDA	Food and drug administration
FP	Finished product
FTIR	Fourier transform infrared
GCP	Good clinical practice
GMP	Good manufacturing practice
HCCF	Harvest cell culture fluid
HCL	Hydrochloric acid
HCP	Host cell protein
HIC-HPLC	Hydrophobic interaction chromatography - high performance liquid chromatography
HMWS	High molecular weight species
ICH	International Conference on Harmonisation
ICP/MS	Inductively coupled plasma mass spectrometry
IEC-HPLC	Ion exchange - high performance liquid chromatography
IgE	Immunoglobulin E

IgG	Immunoglobulin G
IL	Interleukin
IPM	In-process monitoring
IPT	In-process test
ISI	Integrated summary of immunogenicity
LC-MS	Liquid chromatography–mass spectrometry
LLOQ	Lower limit of quantification
LMWS	Low molecular weight species
MAA	Marketing Authorisation Application
MCB	Master cell bank
MMV	Minute virus of mice
MP	Monitored parameter
MSD	Meso scale discovery
Nab	Neutralizing antibody
NBOp	Notified body opinion
NWP	Normalised water permeability
PAR	Proven acceptable range
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PDE	Permitted daily exposure
PFS	Pre-filled syringe
PFS-S	Pre-filled syringe with safety guard
PK	Pharmacokinetics
PPQ	Process performance qualification
PRS	Primary reference standard
PT	Preferred term
QTTP	Quality target product profile
REO-3	Reovirus 3
RMP	Reference medicinal product
SAE	Serious adverse event
SAL	Sterility assurance level
SC	Subcutaneous
SD	Standard deviation
SEC-HPLC	Size exclusion - high performance liquid chromatography
SOC	System organ class
SOP	Standard operating procedure
SPR	Surface plasmon resonance
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse event of special interest
TEM	Transmission electron microscopy
TOC	Total organic carbon
TESAE	Treatment-emergent serious adverse event
Tmax	Time to reach Cmax
uDP	Unassembled drug product
UF/DF	Ultrafiltration/diafiltration
UV	Ultraviolet
VCD	Viable cell density
WCB	Working cell bank
WRS	Workng reference standard
XMULV	Xenotropic Murine leukaemia virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celltrion Healthcare Hungary Kft. submitted on 24 April 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Omlyclo, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indications:

Allergic asthma

Omlyclo is indicated in adults, adolescents and children (6 to <12 years of age).

Omlyclo treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma (see section 4.2).

Adults and adolescents (12 years of age and older)

Omlyclo is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

Children (6 to <12 years of age)

Omlyclo is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

Chronic rhinosinusitis with nasal polyps (CRSwNP)

Omlyclo is indicated as an add-on therapy with intranasal corticosteroids (INC) for the treatment of adults (18 years and above) with severe CRSwNP for whom therapy with INC does not provide adequate disease control.

Chronic spontaneous urticaria (CSU)

Omlyclo is indicated as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal product.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Xolair (Omalizumab), 75 mg, 150 mg, powder and solvent for solution for injection, solution for injection in pre-filled syringe
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 25-10-2005, 20-02-2006, 10-02-2009
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/05/319/001, EU/1/05/319/002, EU/1/05/319/003, EU/1/05/319/004, EU/1/05/319/005, EU/1/05/319/006, EU/1/05/319/007, EU/1/05/319/008, EU/1/05/319/009, EU/1/05/319/010

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Xolair (Omalizumab), 75 mg, 150 mg, powder and solvent for solution for injection, solution for injection in pre-filled syringe
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 25-10-2005, 20-02-2006, 10-02-2009
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Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Xolair (Omalizumab), 75 mg, 150 mg, solution for injection in pre-filled syringe
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 10-02-2009
- Marketing authorisation granted by:
  - Union
  - Union Marketing authorisation numbers: EU/1/05/319/005, EU/1/05/319/008
- Bioavailability study number: CT-P39 1.1

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication

subject to the present application:

Date	**Reference**
28 March 2019	EMA/CHMP/SAWP/175758/2019
17 October 2019 January 2020	EMA/CHMP/SAWP/546616/2019
17 September 2020	EMA/CHMP/SAWP/466038/2020

The scientific advice EMA/CHMP/SAWP/175758/2019 pertained to the following quality, non-clinical, and clinical aspects:

- *Acceptability of the* proposed set of physicochemical and biological tests to demonstrate similarity of CT-P39 to Xolair and suitability of the release and long-term stability test items of active substance and drug products to support the marketing authorisation application for CT-P39.
- Acceptability of non-clinical program to support the clinical development and marketing authorisation application of CT-P39 provided that the physico-chemical and biological comparability is reliably confirmed.
- Acceptability of the randomised, double-blind, two-arm, parallel group, single-dose study to compare the PK and safety of the two omalizumab products (CT-P39 and EU-approved Xolair®); in particular, with respect to study population, dose choosing, primary PK endpoints (AUC_0-last, C_{max} and $AUC_{0\text{-}inf}$), sampling duration, sample size and equivalence margin to support marketing authorisation. Acceptability of the Phase III clinical study in patients with Chronic Spontaneous Urticaria who remain symptomatic despite H1-antihistamine; in particular, agreement with the proposed study design with specific respect to study population, primary efficacy endpoint, secondary endpoints, justification of equivalence margin, sample size and power. Sufficiency the size of the subject population (48 healthy subjects with single dose and 208 patients with CSU over 24 weeks of treatment) to adequately characterise the safety and immunogenicity profile of CT-P39 as a biosimilar product to Xolair® for the purpose of marketing authorisation application to CT-P39. Acceptability of the developing an additional formulation of CT-P39 containing 75 mg and 150 mg lyophilised powder in a single-dose vial for reconstitution assuming previous demonstration of therapeutic equivalence, PK similarity and analytical similarity of CT-P39 150 mg/1 mL PFS to EU approved PFS Xolair 150 mg/1 mL PFS.

The scientific advice EMA/CHMP/SAWP/546616/2019 pertained to the following quality, non-clinical and clinical aspects:

- Proposition to register two devices for CT-P39 drug delivery, a pre-filled syringe (PFS) and PFS with safety guard (PFS-S).
- Conduction of a repeated toxicity study in order to support the clinical trial applications in non-EU jurisdictions and acceptability of not performing the immunogenicity assessment in non-human primate animals as is generally not predictive for immunogenicity in humans.
- Acceptability of the 3-arm Phase I PK equivalence study of CT-P39 with EU-approved and US licensed Xolair® consisting of two parts (the first part is a randomised, double-blind, two-arm (1:1, CT-P39 and EU-approved Xolair), parallel group single-dose study to evaluate safety and PK; the second part is a randomised, double-blind, three-arm (1:1:1, CT-P39, EU-approved Xolair, US-licensed Xolair), parallel group, single-dose study) to demonstrate similarity in PK and

acceptability of the changes made in Phase III clinical study in patients with Chronic Spontaneous Urticaria who remain symptomatic despite H1-antihistamine treatment in comparison to initial scientific advice.

The Scientific advice EMA/CHMP/SAWP/466038/2020 pertained to the clinical aspects:

- Need for human factor studies and clinical usability studies for the PFS in the biosimilar product.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Finbarr Leacy Co-Rapporteur: Maria Concepcion Prieto Yerro

The application was received by the EMA on	24 April 2023
The procedure started on	18 May 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 August 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	18 August 2023
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	21 August 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 September 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 December 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 January 2024
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: A GCP inspection at 3 sites: the sponsor in Korea (Republic of), a clinical site in Korea (Republic of) and a clinical site in Bulgaria between 9 October and 23 November 2023. The outcome of the inspection carried out was issued on	02 February 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 February 2024
The CHMP considered the views of the Biologics Working Party as presented in the minutes of this meeting	14 February 2024
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	15 February 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	22 February 2024

The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 February 2024
The CHMP Rapporteur's Assessment Report was circulated on	06 March 2024
The updated CHMP Rapporteur's Assessment Report was circulated on	14 March 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Omlyclo on	21 March 2024

2. Scientific discussion

2.1. Problem statement

Not applicable.

2.2. About the product

CT-P39 (omalizumab) is a recombinant deoxyribonucleic acid (DNA)-derived humanized monoclonal antibody, of approximately 149 kiloDaltons in mass, which binds to human IgE. Immunoglobulin E is an antibody produced in plasma cells and mediates Type I hypersensitivity by binding Fc receptor on tissue mast cell or blood basophils. Omalizumab belongs to the ATC code R03DX05 that includes drugs for obstructive airway diseases and other systemic drugs for obstructive airway diseases.

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-bound IgE. By binding to IgE, omalizumab inhibits the binding of antigens to IgE, which inhibits the degranulation process. This action in turn inhibits the release of the various mediators released via degranulation, and as such functions to lessen sensitivity to allergen.

CT-P39 has been developed by Celltrion as a proposed biosimilar to the reference product Xolair (INN: omalizumab), which was authorised via the Centralised Procedure in the European Union on 25/10/2005 (marketing authorisation holder Novartis Europharm Limited). The Applicant is claiming all approved indications of the reference product.

2.3. Type of application and aspects on development

During the development of CT-P39 the applicant sought Scientific Advice (SA) from the EMA Scientific Advice Working Party (SAWP), see section 1.5. Scientific Advice.

Quality

The approach to quality development of CT-P39 is generally acceptable. The applicant was advised (EMEA/H/SA/4063/1/2019/III) to include a statistical approach to comparability for process development. This advice was not adhered to, however, the changes made to the processes (both active substance and finished product) were not considered high risk and the comparability assessments provided was deemed sufficient.

The Applicant sought advice on the strategy to demonstrate biosimilarity at various stage of development and it is acknowledged that the recommendations have been taken into account.

Non-Clinical

The nonclinical development program for CT-P39 was designed to support clinical studies and to demonstrate similarity to EU-approved Xolair (hereafter referred to as "EU-approved Xolair). A comprehensive battery of *in vitro* pharmacodynamic (PD) studies were performed to demonstrate the similarity of CT-P39 and EU-approved Xolair as part of robust chemistry, manufacturing, and control (CMC) program assessment. In addition, an *in vivo* 4-week repeat-dose toxicology study with toxicokinetics (TK) assessment was performed in cynomolgus monkeys to demonstrate the similarity between CT-P39 and EU-approved Xolair. As indicated in the SA, this repeat-dose toxicity study was not strictly necessary for the clinical development and MAA of biosimilars. According to the stepwise approach recommended in the 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1), an *in vivo* study may not be considered necessary if comparability is demonstrated in *in vitro* studies. However, as also noted in the SA, the rationale for this study is to support regulatory requirements in other territories.

Clinical

The clinical development program consists of the following studies: a primary pharmacokinetic (PK) similarity study conducted in healthy subjects (study CT-P39 1.1) and a pivotal phase 3 therapeutic similarity study conducted in patients with chronic spontaneous urticaria (study CT-P39 3.1). The pivotal PK study (CT-P39 1.1) is 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. Study CT-P39 3.1 is a double-blind, randomized, active-controlled, parallel group, phase 3 study to compare efficacy and safety of CT-P39 and Xolair in patients with chronic spontaneous urticaria who remain symptomatic despite H1-antihistamine treatment. The proposed clinical development is considered acceptable since the clinical biosimilarity comparability exercise begin with a PK study and is followed by a clinical efficacy and safety trial.

The clinical development program for CT-P39 has considered the following CHMP guidelines: guideline on similar biological medicinal products, guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues, guideline on the investigation of bioequivalence, guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins and guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins. No deviations have been detected.

Overall, the applicant's approach to the clinical development of this biosimilar is largely acceptable.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a solution for injection in pre-filled syringe containing 75 or 150 milligrams of omalizumab as active substance.

Other ingredients are: L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, Polysorbate 20 and Water for injections.

The product is available in 0.5 ml or 1 ml solution in a pre-filled syringe barrel (type I glass) with staked needle (stainless steel), (type I) plunger stopper and needle cap.

2.4.2. Active substance

2.4.2.1. General information

The active substance (INN omalizumab, also referred to as CT-P39) is a recombinant humanised monoclonal IgG1 antibody. Like other IgG1, CT-P39 is a glycoprotein with one N-linked glycosylation site in the CH2 domain of each heavy chain. Each heavy chain consists of 451 amino acids with 11 cysteine residues, and each light chain consists of 218 amino acids with 5 cysteine residues. However, C-terminal lysine in the heavy chain is post-translationally removed to a large and varying degree in the heavy chain molecules. Therefore, the actual number of amino acids in the heavy chain is considered as 450. The molecular weight of CT-P39 is 146,278 Da.

Omlyclo has been developed as a biosimilar medicinal product to the reference medicinal product (RMP), Xolair.

2.4.2.1. Manufacture, characterisation and process controls

The active substance (AS) is manufactured by Celltrion, Inc., Academy-ro, Yeonsu-gu, Incheon, 22014, Republic of Korea
Sufficient evidence of GMP compliance has been provided for all sites involved in the active substance manufacturing and/or control.

Description of manufacturing process and process controls
The manufacturing process is standard for a monoclonal antibody and is considered to be well described. An overview process flow diagram was provided for the upstream and downstream manufacturing process. Individual process flow diagrams were also provided for each process step and include process parameters and in-process tests.

Critical process parameters and critical in-process tests are indicated. Acceptance criteria ranges or limits are provided for critical and non-critical parameters. Detailed descriptions of each process step are included in the dossier.

A single working cell bank (WCB) vial is expanded in a series of shake flasks and seed bioreactors up to production bioreactor operated in fed-batch mode. Bolus feeds for the production bioreactor are detailed as well as glucose feeds and anti-foam limits. The harvest and recovery process consists of continuous centrifugation, followed by depth and membrane filtration. Microbial and virus testing are carried out on the harvested material. Downstream purification is by affinity chromatography, low pH viral inactivation, anion exchange chromatography, virus filtration, UF/DF, and final filtration and filling into containers for storage. Details of the depth filtration step have been included in the manufacturing process description. Clarification has been provided on the proposed multiple UF/DF cycles expected as part of routine manufacturing. Appropriateness of the sanitisation and regeneration processes have been demonstrated in A.2.

Process holds are proposed following harvest and recovery, affinity chromatography and viral inactivation, anion chromatography, viral filtration, and UF/DF and supported in S.2.5.

Reprocessing is proposed and validation has been provided in S.2.5 with adequate description of the circumstances under which reprocessing will occur.

Control of materials
Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented.

The components of the cell culture media and buffer solutions were provided. The non-compendial components of biological origin used in the commercial manufacturing process include cell culture media, affinity chromatography resin, and anion exchange chromatography resin. The in-house specifications proposed are considered sufficient, and the materials of biological origin are further addressed in A.2.

The source, history and generation of the cell substrate is sufficiently described and, in general, follows the recommendations of ICH Q5B and ICH Q5D. The construction of the expression plasmid is sufficiently described and includes a detailed component map and relevant sequences and cloning strategy. The approach taken is standard. The expression plasmid was fully sequenced after cloning and is presented in the figure below. A safety assessment is provided in 3.2.A.2 for raw materials of animal origin used during cell line generation.

A two-tiered cell banking system is in place. Establishment of the master cell bank (MCB) and working cell bank (WCB) is described in accordance with the ICH Q5D. Date of manufacture, labelling, storage conditions, stability testing and storage locations for the MCB and WCB are sufficiently described. Characterisation of the cell banks has been carried out in line with ICH Q5D. The testing of the cell banks is carried out in accordance with the Ph. Eur. 2031 monoclonal antibodies for human use.

The MCB, WCB and extended cell bank (ECB) were tested for adventitious agents in line with ICH Q5A. The protocol for replacement of the WCB and specifications for qualifying the replacement WCB are considered acceptable.

Control of critical steps and intermediates

In general, the control strategy development is considered to be well described and in line with ICH Q8. The Quality Target Product Profile (QTPP) is based on the finished product and critical quality attributes (CQA) have been established for the AS based on this profile. The CQA are well described and further discussed in P.3.4. The critical process parameters (CPP) and relevant CQA affected by the process parameter are listed in the dossier. A risk analysis of the process parameters that could influence the CQA was carried out in accordance with ICH Q9 and the decision-making process is presented in the dossier. Process parameters were assigned into the relevant group; critical process parameters (CPP), non-CPP, monitored parameter (MP), Critical in-process test (CIPT), IPT, and in-process monitoring (IPM). The definition of the different process variable terminology is provided. The consequences of exceeding the acceptable ranges was described and considered acceptable.

CPP were established based on risk assessment, product knowledge, manufacturing experience and characterisation studies. Suitable justification is provided for the CPP selected and the basis on which process variables were determined to be CPP or non-CPP in the risk assessment exercise. Justification is provided for the proposed target value and acceptable range for the CPP and CIPT. Details of qualified small-scale process characterisation tests on the upstream and downstream processes were provided. Studies characterised potential CPP and their impact on CQA for the production bioreactor step and the downstream purification steps (Affinity chromatography and anion exchange chromatography). Analytical results were statistically evaluated to determine criticality. The proven acceptable range (PARs) were determined for the CPPs and the operating ranges proposed in the control strategy are within the established PARs. A clear explanation has been provided for the proposed CPP and CIPT in the UF/DF process step including additional updates to the reprocessed hold times and range of protein concentration and yield for each reprocessing case.

Additional data to support the viral inactivation and virus filtration parameters are provided in A.2. Bioburden and endotoxin are tested at numerous stages throughout the process and controlled as CIPT. The proposed limits for bioburden and endotoxin are adequately justified. A summary of the

analytical methods used for in-process testing along with the method validation/qualification status for each method is provided.

Process validation
In general, the validation strategy is considered to be appropriate, and the process is under control. Process validation for the AS was carried out at commercial scale the intended AS manufacturing site. Historical manufacturing data were assessed to set operational ranges and acceptable ranges/acceptance criteria for process verification. Upon completion of the process validation runs, process parameters and in-process tests and their acceptance criteria were re-evaluated, and several adjustments were implemented for commercial manufacturing. Overall, there were no batch failures during validation, and all DS results met the proposed criteria. All deviations have been suitably addressed and the process is considered to be under control.

Impurity clearance
The process-related impurities have been addressed using scale-down models and commercial scale batch data. The process parameters of the downstream process scale-down models are considered to be representative of the commercial scale manufacturing process for the affinity chromatography and anion exchange chromatography steps. Impurity clearance studies were performed using a commercial scale batch. In the spiking studies, sufficient clearance of concerned impurities was sufficiently demonstrated. The calculated safety factors are considered sufficient based on the risk assessments provided. Historical batch data also support the propose control strategy.

An acceptable risk assessment on nitrosamine impurities has been provided. Considering the raw materials, manufacturing process and equipment as well as manufacturing environment the risk for nitrosamine impurities is negligible. The details of the risk assessment are provided in Annex 4 of module 1.1 and performed in accordance with the EMA Q&A on Nitrosamines (EMA/409815/2020 Rev.17).

Resin and filter lifetime studies
The proposed chromatography columns maximum number of cycles has been sufficiently supported with data and will be further confirmed at commercial scale. Reported results so far support the conclusion that the that column cleaning is adequate and effective. The overall approach to establishing resin and filter lifetimes is in line with the guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission (EMA/CHMP/BWP/187338/2014) and is acceptable.

Hold times
The proposed process hold times have been sufficiently supported by appropriate data. A sampling and study plan of media and buffer hold studies is provided and is considered representative of the manufacturing process.

Reprocessing
Reprocessing has been described for certain process steps. The reprocessing is non-routine and the conditions for reprocessing have been described in S.2.2. The presented data indicate no impact on product quality as a result of reprocessing and results are reported within the acceptance criteria in place at the time of the study.

Filter validation
All liquid filters used in the manufacturing process were considered in the filter validation. For each filter extractable/leachable tests, chemical compatibility test and bacterial challenge test were evaluated as required.

Freeze/thaw study
Freeze thaw studies were conducted using representative material. The study supports the thawing process and criteria for thaw times are established for the AS container closure system. The results are presented in the dossier and indicate there is no impact on product quality.

Shipping validation
The shipping procedure of the active substance was satisfactorily justified with data from relevant studies.

Manufacturing process development
Several changes have been made throughout development to scale up the manufacturing process. The transition from pilot scale manufacturing process to early versions of the proposed process to the final commercial process and the changes implemented at each stage were sufficiently described and justified; the use of batches manufactured by each process throughout development was also described.

The changes described are supported by two individual comparability studies that included routine release tests and extended characterisation tests using orthogonal state-of-the-art analytical procedures covering the relevant physicochemical and biological characteristics of Omalizumab. Testing was generally performed in a side-by-side manner. In addition, stability data from studies at long-term, intermediate, and accelerated conditions were compared in S.7 and support the conclusions.

Comparability of development processes
Comparability of batches pre- and post-change between each version of the process used in development has been demonstrated considering sufficient number of batches and the approach for establishing comparability in each case is considered acceptable.

Characterisation
Characterisation was provided using state of the art methods. To ensure manufacturing does not affect the quality profile, AS and finished product (FP) were evaluated in side-by-side tests.

Studies were performed to characterise Omlyclo with respect to primary structure, higher order structure, purity/impurity, charge variants, Glycation/glycosylation, protein content and biological characterisation. Brief descriptions of the analytical methods used for characterisation were provided which are acceptable.

Comparability has been clearly demonstrated between the AS and FP demonstrating no effect to the product in manufacturing. The characterisation is considered comprehensive and the physiochemical and biological profile is well described and the approach considered in general to be in accordance with the Guideline on development, production, characterisation and specification for monoclonal antibodies and related products (EMA/CHMP/BWP/532517/2008) and general Ph. Eur. monographs 0784 and 2031.

The formation and controls of product related impurities were sufficiently discussed.

2.4.2.2. Specification

The commercial release specifications have been defined on the basis of process capability and product quality. The control tests proposed for the active substance are considered appropriate to ensure sufficient quality with respect to identity, purity/impurities, quantity, potency and safety (microbial). In general, the panels of tests are in line with ICH Q6B and are considered appropriate for routine control of a monoclonal antibody both at release and shelf life. Release data from a number of AS batches from all variants of the manufacturing processes used throughout development were assessed to

determine the release specifications. The batches were used in non-clinical, clinical, stability, comparability, and commercial validation studies. Acceptable specification limits have been proposed. The methods to test impurities are described and stated to be qualified for their intended purpose.

Analytical procedures and reference standards
Compendial analytical procedures are performed in accordance with the relevant Ph. Eur. The non-compendial methods proposed cover identity, glycosylation, purity/impurity, concentration and potency. In general, the method descriptions are sufficiently detailed, the approach to validation is in accordance with the ICH Q2(R1), and the results meet the proposed acceptance criteria.

Reference standards
The primary reference standard was derived from the active substance batch manufactured and assigned 100 % potency. Requalification testing of the primary reference standard will be carried out and the working reference standard will be used as a reference for Identity by IEC-HPLC, peptide mapping and IgE Binding Inhibition assay. Requalification of the working reference standard will be performed against the primary reference standard. The criteria for introduction of a new primary reference standard includes specifications for the biological activity and statistical rationale for assigning potency to ensure there is no drift from the lot used in the clinical studies which is acceptable. In addition, the applicant has clarified how the requalification protocols for Primary and working reference standard (PRS and WRS respectively) ensure absence of drift with regards to potency. The HCP standard and anti-HCP antibody generation was adequately described for the earlier platform HCP assay and the current process specific HCP assay. Qualification of a replacement process specific HCP reference standard and reagents has been carried out in accordance with the Ph. Eur. 2.6.34.

Batch analysis
Batch data batches manufactured throughout development are presented in the dossier. The data provided are all within the proposed specifications and demonstrate that the commercial process is capable of manufacturing a consistent active substance.

Container closure
The AS is filled into pre-sterilised (gamma irradiated), pyrogen free polycarbonate bottles with a polypropylene cap. Representative certificates of analysis from the vendor are provided.

Specifications for the container/closure system were presented. The container closure integrity test was performed and no leakage was observed.

The applicant cannot declare the materials used in the container closure to be compliant with the Ph. Eur. or the foodstuff legislation. Therefore, compatibility tests are required to assure the suitability of the container for the storage of the AS. The applicant has performed leachables studies applying the ICH M7 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk. The detection methods and conditions are described. A toxicological risk assessment evaluation was performed for a leachable identified and daily exposure is determined to be well below the PDE. Elemental impurities were tested to detect elements listed in ICH Q3D and further elements of interest. In addition, satisfactory evidence demonstrating that the container closure system meets the requirements of Ph. Eur. 3.2.2.1 -plastic containers for aqueous solutions for infusion (appendix 1 – 3.2.S.6) was provided.

2.4.2.3. Stability

Stability data at long-term for up to 48 months, intermediate and at accelerated conditions were provided to support the proposed shelf life. The provided stability data derived from batches produced by a previous variant of the process and the proposed commercial process and packaged in a representative container closure system. Considering that comparability between the manufacturing process variants was sufficiently demonstrated the approach is acceptable.

In addition, photostability study results were provided. It was concluded that the AS should be protected from light.

Testing protocols are provided and are considered acceptable. The analytical methods are the same as those used in the AS release testing and this can be accepted. Suitable justification has been provided to exclude microbial testing from the stability program testing protocol. The stability indicating profile is supported by the accelerated study data.

Overall, the provided AS stability data support the shelf-life of the AS packaged in the proposed container closure and stored at the recommended storage condition. The proposed post-approval stability protocol is considered acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Omlyclo finished product (FP) is supplied as a sterile, preservative-free solution in a 1mL Type I glass pre-filled syringe, with an extractable volume of not less than 1.0 mL or 0.5 mL. The finished product primary container is a pre-filled syringe (PFS) containing CT-P39 and is presented in two strengths: 75 mg or 150 mg. Omlyclo is formulated as a nominal formulation at 150 mg/mL CT-P39All excipients are of pharmacopoeial grade.

Pharmaceutical development
Omlyclo was developed as a similar biological medicinal product to the reference medicinal product (RMP), Xolair. Omalizumab is a recombinant humanised monoclonal antibody that is manufactured using a CHO cell line by fed-batch cell culture, followed by harvest, purification, formulation and subsequent fill-finish operations.

Full details of the formulation history throughout clinical development were presented in the dossier. The same formulation and container closure systems have been used in non-clinical and clinical studies, the applicant has attempted to keep CT-P39 aligned with the reference medicinal product (RMP), Xolair, throughout development. The commercial formulation was used in phase III clinical trials. No novel or unusual excipients are used. The selection of excipients and their concentrations are based on internal prior knowledge/experience, development studies and shipping and freeze/thaw studies. Overall, the applicant has presented a good understanding of each component used in the commercial formulation and justified their inclusion. The robustness of the formulation has been studied and demonstrated.

Manufacturing Process Development
Manufacturing process development from the early development phase to the commercial production has been clearly described. Comparability has been presented for each process change and the main differences have been justified. Comprehensive comparability assessments included extended characterisation, incorporating primary, secondary and tertiary structural analysis, biological activity

and release testing. The comparability assessments are considered sufficient to demonstrate comparability. The approach lacked a statistical element however, as the changes to the process are considered minor this was accepted.

The leachable study revealed an unknown compound above the analytical evaluation threshold (AET) which was attributed to the analysis process as it was also detected in the blank. The applicant has provided supplementary information on the design of the study to demonstrate that the unknown compound is in fact an analysis artifact.

The final, assembled device presentations do not have any contact with the FP and as such no compatibility studies were conducted. It was further demonstrated that the assembly process has no impact on product quality. No preservatives are included in the CT-P39 PFS. Bioburden and endotoxins are routinely tested as IPCs. Sterility and endotoxins are tested at release and over shelf-life.

2.4.3.1. Manufacture of the product and process controls

The manufacturing sites involved in the manufacture of the finished product (FP) were clearly stated. Sufficient evidence of GMP compliance has been provided for all sites involved in the FP substance manufacturing and control.

The manufacturing process of CT-P39 75 mg and 150 mg drug product consists of formulation, sterile filtration, aseptic filling, and visual inspection processes to produce the drug product as an unassembled drug product (uDP) in a pre-filled syringe without plunger rod. Once CT-P39 drug product has been produced as an uDP form, it is assembled into pre-filled syringes with safety guard (PFS-S). The manufacturing processes for both forms are identical in respect to steps, they differ at the aseptic filling and stoppering step in terms of process parameters.

The manufacturing process is standard for therapeutic monoclonal antibodies. The level of detail in the description of the manufacturing process provided by the applicant is adequate. In process hold times have been provided and supported by data provided in P.3.5.

Process controls
All process parameters have designated acceptance criteria, that have been set based on development studies and/or historical manufacturing data and process validation.

Process validation / verification
Process validation was performed on three commercial scale batches produced for both the 75 mg and 150 mg process. The two strengths process differ only at the filling stages, the validation performed for the 150 mg process largely covered the 75 mg process. Satisfactory process validation data was presented covering hold times, filter validation, media fills and shipping. Extensive characterisation and release tests showed that the process produced a consistent product throughout. Based on the provided data, it is indicated that the manufacturing process is capable of consistently produce FP of consistent quality which meets the specifications.

Extensive characterisation and release tests showed that the process produced a consistent product throughout.

Shipping validation of CT-P39 DP via air and ground transportation under refrigerated conditions is considered acceptable. Overall, the data provided demonstrates that the FP manufacturing process is valid, under control and capable of producing material of consistent quality.

2.4.3.2. Product specification

The finished product release specification, cover appearance, pH, safety, identity, purity, content, potency and functionality test. The stability specifications cover appearance, pH, purity, concentration and potency.

Specifications have been included for CT-P39 150 mg and 75 mg unassembled drug product (uDP). Reference is made to the methods used (compendial/in house method number) which is endorsed. All listed specifications are considered comprehensive and therefore acceptable.

Justification of FP acceptance criteria for many tests has been provided in the AS section of the dossier. This is acceptable as, for the most part, the acceptance criteria is the same and because the AS is essentially the same as the FP from a quality perspective.

A risk assessment in accordance with ICH Q3D was conducted for elemental impurities. It was concluded that the risk of exposing the patient to these elements above the threshold limit is low. The applicant's risk assessment for elemental impurities is considered acceptable.

The applicant has provided an overview of the nitrosamines risk evaluation. The risk for the potential sources of nitrosamines were evaluated for the following items: raw materials, recovery of materials, utilities, manufacturing process of media, buffers and solutions, manufacturing process of CT-P39 drug substance/drug product, equipment used for manufacturing CT-P39 drug substance/drug product, master batch record and manufacturing procedures and manufacturing and storage environment. It was concluded that the potential risk for presence of nitrosamines is negligible in CT-P39 AS and FP. As there is no risk identified, confirmatory testing is not considered necessary, neither are any additional control measures.

Analytical procedures and reference standards
Method descriptions are provided for the PFS for container closure integrity and break-loose glide force. The method descriptions are described in sufficient detail. All other analytical procedures are either common to testing of both AS and FP and thus provided in Section 3.2.S.4.2 or are compendial methods.

For methods common to both testing AS and FP, no additional validation is performed; this is acceptable. For Ph. Eur. methods specific to FP testing (sterility and endotoxins) product specific qualification was performed and showed that CT-P39 does not interfere with method performance. Container closure integrity, break loose glide force tests were validated in accordance with ICH Q2 (R1).

The same reference standard is used to release test both AS and FP. Given that the methods are the same and the formulation is unchanged from AS to FP, this is acceptable.

Batch analysis
Batch analysis data was provided for ten 150 mg and three 75 mg FP batches manufactured. All presented batch data met the proposed specifications in place at the time of testing. The batch analysis data presented for the PPQ batches complies with the limits in the proposed commercial FP specification. Results from FP lots show consistency and uniformity of the product and indicate that the process is under control.

Container closure
The primary packaging for the FP consists of a 1 mL long Type I glass PFS fitted with a staked 27G, ½" special thin wall needle. The components of Omlyclo primary packaging comply with the requirements of the relevant Ph. Eur. monographs and ISO 10993. The choice of container closure system has been

demonstrated and is supported by functionality and compatibility studies. In general, adequate descriptions have been provided for the container closure system components, including supplier specifications, technical drawings and dimensions. No CE mark or Notified Body opinion (NBOp) was provided for the pre-filled syringe device in the initial submission. This was raised as a Major Objection by the CHMP. The applicant in their responses provided NBOp and the device is confirmed to be in full compliance with the relevant General Safety and Performance Requirements (GSPRs) in Annex I of Regulation (EU) 2017/745, thus resolving the MO.

The glass barrel used complies with Ph. Eur. 3.2.1 (Glass Containers For Pharmaceutical Use), the stopper and shield comply with Ph. Eur. 3.2.9 (Rubber Closures For Containers For Aqueous Parenteral Preparations), this is endorsed.

Sufficient details regarding the sterilisation methods for the staked needle were provided.

2.4.3.3. Stability of the product

Based on available stability data, the shelf life and storage conditions as stated in the SmPC (24 months in refrigerator (2 °C – 8 °C)) are acceptable. The product should not be frozen, and should be protected from light.

Stability studies have been performed under long term conditions at 5 ± 3 °C and under accelerated conditions (25 ± 2°C / 60 ± 5% RH) in accordance with current ICH guidelines. The samples used in the stability studies are the uDP.

The provided stability data derived from batches produced by a previous variant of the process and the proposed commercial process and packaged in the proposed container closure system. Considering that comparability between the manufacturing process variants was sufficiently demonstrated the approach is acceptable.

Stability of additional storage at room temperature (up to 25 °C) after long term storage at 5 °C was evaluated and the results confirm that CT-P39 is stable for up to 7 days at room temperature when removed from refrigerated conditions.

The proposed shelf life is further supported with data from stressed studies. Supportive data regarding temperature cycling is also provided to support temperature excursions and is considered acceptable.

A photostability study, performed according to ICH Q1B, demonstrating that CT-P39 is sensitive to light exposure, and the relevant precaution is included in the product information (SmPC section 6.4).

2.4.3.4. Biosimilarity

Analytical similarity of CT-P39 was assessed in a comprehensive similarity exercise using EU-sourced Xolair as reference medicinal product (RMP). The comparability assessment was, for the most part, conducted as per the relevant EU guidelines on the development of similar biological medicinal products (CHMP/437/04 Rev 1, EMA/CHMP/BWP/247713/2012), as well as the principles of comparability as per ICH Q5E.

The 2-way analysis included batches of EU-approved Xolair, and batches of CT-P39. The CT-P39 and EU-approved Xolair lots were analysed in the analytical similarity studies. It is agreed that the batches used are well spread, covering different ages across the shelf life with sufficient overlap between both products. Overall, the applicant's approach for the side-by-side comparison while demonstrating that storage does not impact the quality of stored batches has been accepted as for other EU approved biosimilars.

The similarity ranges were established using data from analysis of EU-approved Xolair batches. The approaches to compare physicochemical characteristics and biological quality attributes were described. The data is clearly presented no concerns were raised regarding the approaches used.

Two-way Similarity Assessment

The selected comprehensive set of orthogonal state-of-the–art analytical methods, which covers primary and higher order structure, post-translational modifications, size and charge variants, protein concentration, as well as Fab and Fc-mediated biological functions, appears adequate to address the relevant quality attributes of omalizumab. It is agreed that the chosen methods are suitable to characterise and compare the most relevant physicochemical and biological quality attributes of the Omalizumab molecule. Following a query raised at D120, The Applicant has included orthogonal methods as recommended in scientific advice EMEA/H/SA/4063/1/2019/III (amino acid composition analysis and particulate matter) in the comparative assessment as requested. The attributes and analytical techniques used in the analytical similarity assessment are shown in table below.

Table 1: Summary Data for the 2-way Biosimilarity Assessment Quality Attribute

Summary Data for the 2-way Biosimilarity Assessment Quality Attribute		**Tests/Methods**	**Analytical Similarity Summary**
Primary Structure	Intact Mass (Non-reduced)	LC-MS	Similar
	Intact Mass (Reduced)	LC-MS	Similar
	Peptide Mapping (Sequence Coverage)	LC-MS/MS	Identical
Post-translational Modifications	Peptide Mapping (Modification)	Deamidation by LC-MS/MS	CT-P39 had lower levels of deamidation but the difference was small and a lower level would not adversely impact efficacy or safety.
		Oxidation by LC-MS/MS	Similar
		N-terminal Glutamic Acid Variant by LC-MS/MS	CT-P39 had slightly lower level of pyro-glutamic acid but the difference is small and a lower level would not have an adverse effect on clinical safety or efficacy.
		C-terminal Lysine Variant by LC-MS/MS	CT-P39 showed higher level of heavy chain with C-terminal lysine than EU-approved Xolair®, difference justified.
		Isomerization Variant by LC-MS/MS	CT-P39 had slightly lower levels of aspartate isomerization variants than EU-approved Xolair®, difference justified.
	N-terminal and C-terminal Sequencing	LC-MS/MS	Identical
Physicochemical Analyzes	Charge Variants	icIEF	CT-P39 and EU-approved Xolair® had similar icIEF electropherogram profiles and the same peaks were detected. The pI of each peak was the same in each of the products.

Summary Data for the 2-way Biosimilarity Assessment Quality Attribute		Tests/Methods	Analytical Similarity Summary
		IEC-HPLC	CT-P39 and EU-approved Xolair® had similar charge isoform peak distributions. The 2 products generally contain the same isoform peaks. Some minor differences between CT-P39 and EU-approved Xolair® in levels of isoform groups were noted in the relative proportion of the IEC-HPLC peaks, difference justified.
Glycation and Glycosylation	Glycation	LC-MS	CT-P39 had a slightly lower level of glycation in light chain and heavy chain than EU-approved Xolair®. The slightly lower level of glycation in CT-P39 is highly unlikely to have an adverse impact on efficacy or safety.
	Glycosylation	Oligosaccharide by UPLC	CT-P39 had slightly higher high mannose glycan portion than EU-approved Xolair®, difference justified.
		N-linked Glycan analysis	
Purity/Impurity	Size Variants	SEC-HPLC	CT-P39 has very slightly lower levels of monomer and higher levels of LMW species than EU-approved Xolair®. However, the differences are so small and therefore, have no clinically meaningful impact.
		SEC-MALS	Similar
		AUC	CT-P39 showed slightly lower %HMW than EU-approved Xolair®
		CE-SDS (Non-reduced)	CT-P39 has slightly lower levels of intact IgG than EU-approved Xolair®. The difference is too small to have any significant clinical impact.
		CE-SDS (Reduced)	CT-P39 has a slightly lower level of LC+HC than EU-approved Xolair®, difference justified.
	Aspartate Isomerization	Papain/HIC-HPLC	EU-approved Xolair® and CT-P39 contain the same or similar isomerization. There were some minor differences in the relative proportions of the peaks and the levels of isomerization and free

Summary Data for the 2-way Biosimilarity Assessment Quality Attribute		Tests/Methods	Analytical Similarity Summary
			thiol were lower in CT-P39 than EU-approved Xolair®.
Higher Order Structure	Secondary	CD (Near-UV)	Similar
		CD (Far-UV)	Similar
		FT-IR	Similar
	Tertiary, including free thiol and disulfide bonds	DSC	Similar
		Ellman's assay	CT-P39 had slightly lower levels of free thiols than EU-approved Xolair®.
		LC-MS/MS (disulfide bond)	Identical
Content	Protein Concentration	UV_{280}	Similar
Biological Analysis	Fab binding	IgE Binding Assay (ELISA)	Similar
		IgE Binding Inhibition Assay (ELISA)	Similar
		Cell-based IgE Binding Inhibition Assay (CELISA)	Similar
		Beta-Hexosaminidae Release Inhibition Assay	Similar
		IgE-FcεRII Binding Inhibition Assay (ELISA)	Similar
	Fc binding	C1q Binding Assay (ELISA)	Similar
		FcγRIIIa (V-type) Binding Affinity (SPR)	CT-P39 had higher FcγRIIIa (V type) binding affinities than EU-approved Xolair®, difference justified.
		FcγRIIIa (F-type) Binding Affinity (SPR)	Similar
		FcγRIIIb Binding Assay (SPR)	Similar
		FcγRIIa Binding Affinity (SPR)	Similar
		FcγRIIb Binding Affinity (SPR)	Similar
		FcγRI Binding Affinity (SPR)	Similar
		FcRn Binding Affinity (SPR)	Similar

Physicochemical Analysis

CT-P39 and EU-approved Xolair have similar intact mass. Amino acid sequence coverage was confirmed to be identical for both products having the same N- and C-terminal sequences. Post-translational modification (PTM) analysis by peptide mapping included deamidation, oxidation, N-terminal pyroglutamic acid variants and C-terminal lysine variants. In general, the results for the other PTM analysis showed both products contain similar variants with minor quantitative differences. The observed differences are small and adequate justification based on scientific literature was included for each PTM for the lack of potential clinical relevance / impact. Where needed additional supportive data were presented to show observed do not have an impact on IgE binding thus unlikely to affect biological activities in vivo.

The icIEF electropherograms show a similar pattern in all batches of both products with the same peaks identified. Similarly, IEC-HPLC data presented shows EU-approved Xolair and CT-P39 generally contain the same charge isoform peaks. Some differences were observed but the applicant´s conclusion that these differences are unlikely to affect safety or efficacy is agreed.

CT-P39 was shown to have lower level of glycation of both the LC and HC. The Applicant justified that this difference is not likely to have an adverse effect on efficacy considering the binding regions. This hypothesis is supported by the biological activity study results hence is agreeable.

A comparison of glycosylation patterns was assessed by UPLC and the type and amount of N-glycans attached to peptides was assessed. In general, comparable profiles were shown and the same major glycoform groups were detected in both products.

Extensive comparative data is provided on size variants, molecular weight of size variants and the amount of intact IgG and sum of HC+LC. No new size variants are observed for CT-P39 following the various methods assessed. For purity/impurity by CE-SDS some minor differences were observed, notably intact IgG (non-reduced) and %LC+HC (reduced) of CT-P39 is slightly lower with a corresponding increase in the levels of %NGHC compared to EU-approved Xolair. The Applicant has provided sufficient supportive evidence to show these differences have no clinical impact.

Papain/HIC-HPLC analysis was also presented and while the same isomerisation and free thiol variants were identified in each product differences were observed in the relative proportions of the peaks and the levels of isomerization and free thiol between CT-P39 than EU-approved Xolair. Adequate discussion of the differences is provided (including supportive batch age studies) and it is agreed the differences are unlikely to significantly affect biological activities *in vivo*.

Higher order structure of CT-P39 and EU-approved Xolair was studied by DSC, far- and near-UV CD, FTIR and disulphide bonds. The results are highly similar amongst all batches analysed. Quantity is based on protein content determined by UV-spectrometry. The extinction coefficient has been determined experimentally. CT-P39 and EU-approved Xolair are similar in their protein concentration.

Biological activity

An extensive array of different biological activities was compared for EU-approved Xolair and CT-P39. The Fab-mediated MoA was evaluated by a range of *in vitro* biological assays at different levels (binding to IgE (ELISA), inhibition of IgE bind to FcεRI (ELISA), inhibition of IgE binding to FcεRI on cells (CELISA), inhibition of beta-hexosaminidase release and inhibition of IgE binding to FcεRII (ELISA)). Biological characteristics were further compared with regard to all the different Fc gamma receptors (I, IIa, IIb, IIIa and IIIb), FcRn and C1q binding. In general, the data presented from all the Fab binding mediated tests are all highly comparable. For all biological activity assays CT-P39 batch values fall within the quality range of EU-approved Xolair batches, with the exception of the FcγRIIIa (V-type) binding assay. Given that ADCC is not a relevant MoA, it is agreed this difference is unlikely to be clinically meaningful.

Forced stability/additional characterisation

Additional characterisation of the product-related variants and impurities, impact of aglycosylation, and additional MoA studies were performed to supports the applicant's conclusion that any differences observed in the comparative assessment have no significant impact on biological activities and therefore have no clinically meaningful impact.

A forced degradation study was also performed, and the results show that the rates and levels of degradants were similar between the two products.

Analytical Methods

Summaries of the methods used in the comparative analytical assessment studies, including details of the principles of the method, sample preparation, the equipment (including relevant parameters) and critical reagents used are provided in the dossier. In addition to the method descriptions the applicant has presented summary tables for the method qualifications.

Overall conclusions
The comparative analytical assessment demonstrated that the primary and higher order structure, functional binding, and bioactivity of CT-P39 is highly comparable to EU-approved Xolair. For C-terminal lysine variants, charge, and purity/impurities, some minor differences were observed. However, any differences identified were considered minor and were in general sufficiently justified by the applicant, hence do not impact on the biosimilarity claim. Based on the data presented the claim of biosimilarity is supported.

2.4.3.5. Adventitious agents

The strategy to control adventitious agents consists of controlling potential sources of virus contamination both to the cell bank system and the production process, and viral clearance processes and is well described. The microbial safety of the drug substance and drug product is controlled throughout the manufacturing process and at release. Testing for sterility and mycoplasma on the MCB and WCB are performed in accordance with the Ph. Eur. 2.6.1 and 2.6.7 respectively and details are provided in S.2.3. The unprocessed bulk is tested for mycoplasma in accordance with the Ph. Eur. and the batches tested to date were free from mycoplasma. The applicant confirmed that testing of the end of production cell bank (EPCB) for sterility was carried out in accordance with the Ph. Eur. 2.6.1 or equivalent.

The applicant's determination that there is a minimal risk of TSE contamination can be supported. Valid TSE CEPs were provided. Valid TSE CEPs were provided for media used in the cell line development. The cell culture media for routine manufacturing is derived from both non-TSE relevant species and TSE relevant source. A TSE CEP is provided for the TSE relevant source.

The TSE risk assessment has been updated to include materials that come into direct contact with the equipment used in manufacture of the medicinal product or that come in contact with the medicinal product and is acceptable.

The cell banking system manufacturing and characterisation is described in S.2.3. Results of the viral testing is provided and indicate the MCB and WCB are free of adventitious viral agents. The testing performed on the MCB, WCB and EPCB is considered to be in accordance with the ICH Q5A (R1). Testing on the unprocessed bulk included adventitious virus testing and the results are acceptable.

The design of the viral clearance study is clearly presented and considered to be in accordance with ICH Q5A. The model virus used represent a range of virus types and characteristics. The viral clearance steps are identified as the low pH treatment (viral inactivation), two chromatographic unit operations, protein A and anion exchange, and the nanofiltration (viral filter) step. Qualified scaled down models are used in spiking studies and are considered representative of the manufacturing process (see also S.2.5).

Batches pre-and post-change between each version of the process were used in the studies and comparability of these processes was demonstrated in S.2.6 and this approach is acceptable. Worst-case conditions and operational limits used in the studies are described and considered adequately supported. Runs were carried out in duplicate including an additional run using aged resin in the chromatography steps. The aged resin was tested in the virus carry-over study and indicates that the regeneration and sanitisation processes are sufficient.

The safety margin calculated for the Retrovirus-like particles clearance demonstrates that the process clearance capacity provides an adequate safety margin.

2.4.3.6. GMO

Not applicable.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. A MO was raised during the procedure in relation to the missing NBOp for the proposed devices; the NBOp was provided during the procedure and the MO was resolved. Overall, the available quality data support biosimilarity versus EU-approved Xolair. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Satisfactory information has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

This is an application submitted by Celltrion Healthcare Kft. under Article 10(4) of Directive 2001/83/EC, as amended for Omlyclo (CT-P39), a proposed biosimilar of the European reference product Xolair (omalizumab; Novartis Europharm Limited). Omlyclo is a solution for injection in pre-filled syringe available in 150mg and 75mg strengths for subcutaneous use.

2.5.2. Pharmacology

Omalizumab is a humanized monoclonal antibody that selectively binds to human immunoglobulin E (IgE) and prevents binding of IgE to FcεRI (high-affinity IgE receptor) on basophils and mast cells, thereby reducing the amount of free IgE that is available to trigger the allergic cascade. Treatment with omalizumab also reduces the number of FcεRI receptors on basophils in atopic patients.

A comprehensive battery of two-way *in vitro* PD similarity studies was performed to demonstrate similarity between CT-P39 with EU-approved Xolair. The assessment of biosimilarity of CT-P39 is primarily based on the quality assessment of the appropriateness and acceptability of the *in vitro* comparability studies conducted. No significant differences are reported between CT-P39 and EU-approved Xolair.

No *in vivo* PD studies has been undertaken by the applicant. The primary PD effect on total IgE and free IgE levels was evaluated *in vivo* in a 4-week GLP-compliant repeated toxicity study in cynomolgus monkeys. Increases in total IgE levels were noted on Day 8 and 29 in animals administered with 5 or 75 mg/kg/week EU-approved Xolair or CT-P39, compared to controls. The IgE level changes (increase in total IgE and decrease in free IgE) after administration of CT-P39 and EU-approved Xolair were an expected pharmacological effect of omalizumab and were similar between the CT-P39 and EU-approved Xolair treatment groups, supporting the similarity of CT-P39 and EU-approved Xolair.

No secondary pharmacology, PD drug-drug interaction or safety pharmacology studies have been performed.

2.5.3. Pharmacokinetics

No stand-alone PK studies have been performed, comparative toxicokinetic (TK) assessments were incorporated into the 4-week repeat-dose toxicity study. The exposure to CT-P39 or EU-approved Xolair following once weekly (Days 1, 8, 15 and 22) SC injection at 0, 5 or 75 mg/kg during the 4-week toxicity study was assessed in cynomolgus monkeys (n=3/sex/group; Study No. 8401280).

Sex differences of mean omalizumab C_{max} and $AUC_{0\text{-}168hr}$ values were less than 2-fold for CT-P39 and EU-approved Xolair, so results were presented based on combined sex values. After SC injection of CT-P39 or EU-approved Xolair, exposure as assessed by mean omalizumab C_{max} and $AUC_{0\text{-}168hr}$ values, similarly increased with increased dose level from 5 to 75 mg/kg/week. Accumulation was observed after multiple doses of both CT-P39 or EU-approved Xolair in cynomolgus monkeys in a similar pattern. In addition, no reduction in exposure after multiple doses consistent with an ADA effect was observed following administration of either CT-P39 or EU-approved Xolair at 5 or 75 mg/kg.

No distribution, metabolism, excretion or PK interaction studies have been performed.

2.5.4. Toxicology

A comparative *in vivo* toxicology study was conducted to provide complementary information to support the quality assessment of biosimilar comparability.

The toxicity profiles of CT-P39 and EU-approved Xolair were compared in cynomolgus monkeys via once weekly subcutaneous administration for 4 weeks at doses of 5 and 75mg/kg/dose (Study No. 8401278). Binding affinities of CT-P39 and EU-approved Xolair to monkey immunoglobulin E (IgE) have not been evaluated. Both products were well-tolerated, a mild decreased platelet count was reported on Day 26 only in animals administered with 75 mg/kg/week EU-approved Xolair, but no secondary clinical effects or correlated anatomic pathology findings were reported and this finding was considered non-adverse. No other notable toxicologically relevant differences are reported between the two products and these data were generally considered supportive of the similarity between CT-P39 and EU-approved Xolair.

No genotoxicity, reproductive toxicology or carcinogenicity studies have been performed. Local tolerance was assessed as part of the comparative 4-week repeat dose toxicity study. No findings of note are reported.

2.5.5. Ecotoxicity/environmental risk assessment

The applicant has provided a justification for the absence of ERA studies, on the basis that omlyclo is a monoclonal antibody and classified as a protein, therefore a significant risk to the environment is not anticipated. This is acceptable in line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2[1]*).

2.5.6. Discussion on non-clinical aspects

The nonclinical dossier submitted in support of this MAA for Omlyclo (CT-P39), a proposed biosimilar of the European reference product Xolair (omalizumab) includes a comprehensive battery of two-way *in vitro* pharmacodynamic similarity studies, performed to demonstrate similarity between Omlyclo and EU-approved Xolair. The assessment of biosimilarity of Omlyclo is primarily based on the quality assessment of the *in vitro* comparability studies conducted. No significant differences are reported between Omlyclo and EU-approved Xolair.

No *in vivo* PD studies, secondary pharmacology, PD drug-drug interaction or safety pharmacology studies have been undertaken by the applicant. In addition, no absorption, distribution, metabolism, excretion, or PK interaction studies have been performed in support of this MAA. This is acceptable and in line with the EMAs 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues' (EMEA/CHMP/BMWP/42832/2005 Rev1).

A comparative *in vivo* toxicology study was submitted by the applicant, providing complementary information to support the quality assessment of biosimilar comparability between Omlyclo and EU-approved Xolair. The toxicity profiles of Omlyclo and EU-approved Xolair were compared in a GLP compliant 4 week study in cynomolgus monkeys, in which once weekly subcutaneous administration of Omlyclo or EU-approved Xolair were well-tolerated and no toxicologically relevant differences were reported between the two products with the exception of an unexplained, mild decreased platelet count in high dose EU-approved Xolair treated animals only on Day 26, although there was no secondary clinical effects or correlated anatomic pathology findings observed. The decrease of platelet in monkeys is properly described in Part II of the Risk Management Plan (RMP).
The primary PD effect on total IgE and free IgE levels was also evaluated in this study. IgE level changes (increase in total IgE and decrease in free IgE) after administration of CT-P39 and EU-approved Xolair were an expected pharmacological effect of omalizumab and were similar between the CT-P39 and EU-approved Xolair treatment groups, supporting the similarity of CT-P39 and EU-approved Xolair.
Comparative toxicokinetic assessments were also incorporated into this study. The exposure to Omlyclo or EU-approved Xolair similarly increased with increased dose level and accumulation was observed after multiple doses of both CT-P39 or EU-approved Xolair in cynomolgus monkeys in a similar pattern, supporting the similarity in pharmacokinetic parameters between Omlyclo and EU-approved Xolair. Considering all available data, this study was considered supportive of the similarity between Omlyclo and EU-approved Xolair.

No genotoxicity, reproductive toxicology or carcinogenicity studies have been performed, which is acceptable in line with relevant guidance (EMEA/CHMP/BMWP/42832/2005 Rev1). Local tolerance was assessed as part of the comparative 4-week repeat dose toxicity study. No findings of note are reported.

The nonclinical information included in Sections 4.6 and 5.3 of the SmPC is identical to the EU reference product, Xolair, which is acceptable.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, omalizumab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Overall, the available non-clinical data support the biosimilarity of Omlyclo versus the EU reference product Xolair. The MAA for Omlyclo is acceptable from a non-clinical perspective.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Study	Population	Design	Objectives	Study Treatment
CT-P39 1.1 (Pivotal PK study)	Healthy subjects Randomized: 176 <u>Part 1</u> CT-P39 150 mg: 15 EU-approved Xolair 150 mg: 15 <u>Part 2</u> CT-P39 150 mg: 47 EU-approved Xolair 150 mg: 49 US-licensed Xolair 150 mg: 50	Phase 1, randomized, double-blind, three arm, parallel group, single-dose study to compare the PK and safety of three formulations of omalizumab (CT-P39, EU-approved Xolair, and US-licensed Xolair)	**Primary Objective (Part 2):** • To demonstrate PK similarity in terms of $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and 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:** <u>Part 1</u> • To evaluate initial safety up to Day 29 in terms of TEAE of CT-P39, compared to that of EU-approved Xolair in healthy subjects • To assess additional safety, PK, and immunogenicity of CT-P39 and EU-approved Xolair in healthy subjects up to Day 29 <u>Both parts</u> • To assess additional safety, PK, PD, and immunogenicity of CT-P39, EU-approved Xolair, and US-licensed Xolair in healthy	**Test product:** CT-P39, 150 mg/1 mL by SC injection to the upper arm via PFS as a single administration. **Reference product:** EU-approved Xolair, 150 mg/1 mL by SC injection to the upper arm via PFS as a single administration US-licensed Xolair, 150 mg/1 mL by SC injection to the upper arm via

			subjects up to Day 127	
Study	**Population**	**Design**	**Objectives**	**Study Treatment**
CT-P39 3.1 (Comparative efficacy and safety study)	CSU patients Randomized: 634 <u>Randomized Set: 619</u> • Arm 1: 204 • Arm 2: 205 • Arm 3: 107 • Arm 4: 103 <u>Randomized Set - Treatment Period II</u> Subset: 579 • Arm 1: 187 • Arm 2-1: 96 • Arm 2-2: 97 • Arm 3: 101 • Arm 4: 98	Double-blind, randomized, active controlled, parallel group, Phase 3 study to compare efficacy and safety of CT-P39 and Xolair	**Primary Objective:** • To demonstrate the equivalence of CT-P39 to Xolair at a dose of 300 mg in terms of efficacy in patients with CSU as determined by change from baseline in ISS7 at Week 12 **Secondary Objectives:** • To evaluate relative potency and dose response in terms of efficacy between 300 mg and 150 mg for CT-P39 and Xolair • To evaluate additional efficacy of CT-P39 and Xolair at each dose level of 300 mg and 150 mg • To evaluate the PK, QoL, safety, and immunogenicity of CT-P39 and Xolair	**Treatment Period I (12 weeks):** Three doses of CT-P39 or Xolair as SC injections using a PFS every 4 weeks (Q4W) (at Weeks 0, 4 and 8) • Arm 1: CT-P39 300 mg • Arm 2: Xolair 300 mg • Arm 3: CT-P39 150 mg • Arm 4: Xolair 150 mg **Treatment Period II (12 weeks):** Three doses of study drug 300 mg Q4W (at Weeks 12, 16 and 20) • Arm 1: CT-P39 300 mg • Arm 2-1: CT-P39 300 mg • Arm 2-2: Xolair 300 mg • Arm 3: CT-P39 300 mg • Arm 4: Xolair 300 mg All patients continued to concomitantly receive an approved dose of nonsedating H1-antihistamine.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Analytical methods

The analytical methods used during the clinical development include methods for measuring human serum levels of the active substance of CT-P39, EU-approved Xolair and US-licensed Xolair, anti-drug antibodies (ADA), neutralising antibodies (NAb), as well as Free IgE and Total IgE. The methods have been suitably validated in line with the relevant guidelines.

Bioequivalence

Study CT-P39 1.1

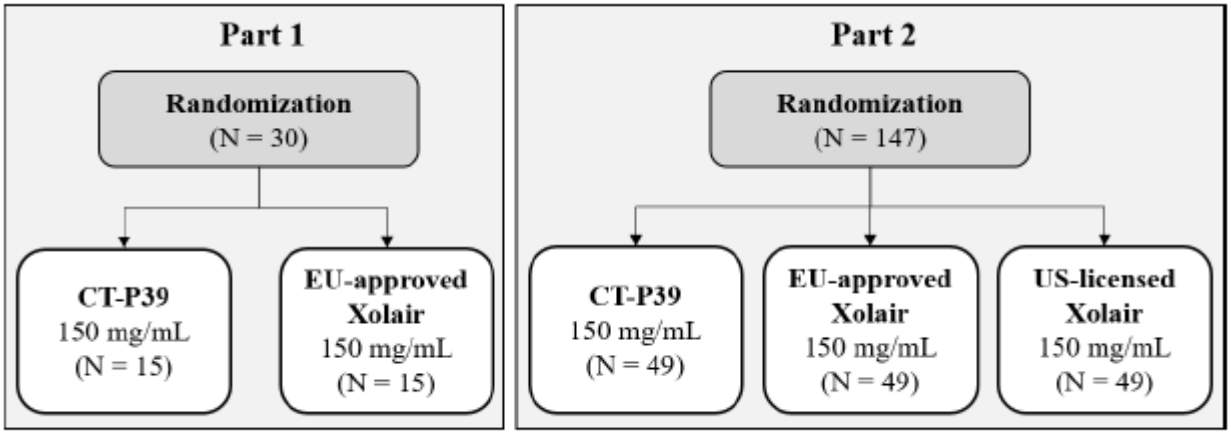
Methods

This was a phase 1, randomised, double-blind, three-arm, parallel group, single-dose, active comparator study, designed to evaluate the safety, PK, PD, and immunogenicity of CT-P39 compared to those of EU-approved Xolair and US-licensed Xolair in healthy subjects.

This study was planned to be conducted in two parts in 177 subjects. The first 30 subjects were to be enrolled in Part 1 to compare the initial safety and randomised in a 1:1 ratio to receive a single dose (150 mg) of CT-P39 or EU-approved Xolair, and 147 subjects were planned to 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 were planned to undergo the same assessments. However, each part was conducted independently, and the result of Part 1 did not affect the progression into Part 2. The data for each part was analysed and presented separately.

The study included screening period (Day -28 to Day -2), admission (Day -1), study period (Day 1 to Day 126), and end-of-study (EOS [Day 127]) visit.



Abbreviations: n, number of subjects; EU, European Union; US, United States.

Figure 1. Schematic of Study Design

Key inclusion criteria

Subjects were eligible to be included in the study only if all of the following criteria applied at any time starting from Screening up to Day 1 prior to IP administration:

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/m2 and 32.0 kg/m2 (both inclusive).

3. Subject with a total IgE level of ≤100 IU/mL at screening.

Key exclusion criteria

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

Treatments

On Day 1, subjects who met all the inclusion and none of the exclusion criteria were randomly assigned to treatment groups according to the randomization scheme.

146 subjects enrolled in Part 2 were randomized (1:1:1) into 3 treatment groups as follows;

- Treatment Group 1: CT-P39, 150 mg/1 mL by SC injection via PFS as a single administration
- Treatment Group 2: EU-approved Xolair, 150 mg/1 mL by SC injection via PFS as a single administration
- Treatment Group 3: US-licensed Xolair, 150 mg/1 mL by SC injection via PFS as a single administration

The dose of 150 mg omalizumab in CT-P39 and the two reference products was selected as flat dose of 150 mg was considered sufficient to support all approved doses. The dose of 150 mg is within the dose range of omalizumab showing linear PK behaviour, reported as 75 mg to 600 mg following administration of a single SC dose. Also, this dose falls within the approved dose range for omalizumab. This is the dose recommended for patients with allergic asthma or nasal polys whose baseline IgE levels are ≤100 IU/mL and body weights are >40 to ≤90 kg.

Table 2: Investigational Product Details

Study Drugs Used in the Study

Product	Supplied as	Lot Number (Expiry Date)
CT-P39	PFS containing 150 mg/mL of omalizumab	CTP39CLN2 (Mar 2021)
EU-approved Xolair	PFS containing 150 mg/mL of omalizumab	AVXS234905 (Sep 2020) AVXS241303 (Mar 2021)
US-licensed Xolair	PFS containing 150 mg/mL of omalizumab	3316571 (Dec 2020)

Abbreviations: EU, European Union; PFS, pre-filled syringe; US, United States.

Objectives

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).

The similarity of PK for each comparison, CT-P39 *versus* EU-approved Xolair, CT-P39 *versus* US-licensed Xolair, and EU-approved Xolair *versus* US-licensed Xolair, was concluded if all 90% CIs of the ratios of geometric means were entirely contained within 80% to 125% for $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max} for Part 2.

Secondary objectives:

Part 2:

- 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.

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, and immunogenicity of CT-P39 and EU-approved Xolair in healthy subjects up to Day 29.

Outcomes/endpoints

Primary endpoints (Part 2)

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

Secondary endpoints:

- Time to C_{max} (T_{max})
- Terminal elimination half-life ($t_{1/2}$)
- Percentage of $AUC_{0\text{-inf}}$ obtained by extrapolation (%AUCext)
- Terminal elimination rate constant (λz)
- Apparent total body clearance (CL/F)
- Apparent volume of distribution during the terminal phase (Vz/F)
- The endpoints for Free IgE were:
    - Minimum serum concentration (C_{min})
    - Time to Cmin (T_{min})
    - Maximum percentage decrease in serum free IgE concentration from baseline (max % decrease)
- The endpoints for total IgE were:
    - C_{max}
    - T_{max}
    - Maximum percentage increase in serum total IgE concentration from baseline (max % increase)

- The safety variables included adverse events, hypersensitivity monitoring, injection site reaction monitoring, vital sign measurements, physical examination findings, clinical laboratory results, twelve-lead ECG, local injection site pain, incidence of ADAs and NAbs

For Part 1, following parameters were analysed as secondary PK parameters additionally:

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

Sampling time points

Blood samples for PK analyses were collected pre-dose, the post-dose at Days 1, 2, 3, 4, 6, 8, 11, 15, 22, 29, 43, 57, 71, 85, 106, and at EoS Day 127.

An additional blood sample was during the screening phase for Serum Total IgE, and then Serum Total and Serum Free IgE blood samples were taken on the same days as blood samples for PK analyses.

Blood samples for immunogenicity were collected pre-dose, then post-dose on Day 15, Day 43, Day 85, and at EoS Day 127.

Sample Size

For Part 2, 147 healthy subjects were planned to be enrolled. To provide 90% statistical power to show that the 90% CIs 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, 126 subjects (42 in each group) with evaluable data in the primary PK Set were required; accounting for drop-out rate of 15%, 147 subjects (49 in each group) were required to be enrolled.

Randomisation

The randomization code was generated by Syneos Health, Inc. prior to the study. For both study parts, subjects were 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 was 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.

Blinding

The study was performed in a double-blind manner. The randomization codes were not revealed to study subjects, investigators, or study centre personnel except for the pre-defined unblinded personnel. Under normal circumstances, the blind had not to be broken.

As this was a 2-part study, it was planned in the protocol that the overall randomization code for each part was broken for reporting purposes, respectively. The randomization codes of Part 1 subjects were revealed to pre-defined unblinded personnel for this reporting (28 August 2020). The investigators, subjects and pre-defined blind personnel from the sponsor and contract research organization were remained blind for Part 1 until the study termination, and the blinding of Part 2 was maintained throughout the study until the database finalization (03 June 2021) for this final CSR.

Statistical Analysis

Analysis populations

Intent-to-treat set: The Intent-to-treat (ITT) Set was 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 were assigned to treatment groups based on randomization.

Pharmacokinetic set: The PK Set was defined as all subjects who received a complete dose of study drug (CT-P39, EU-approved Xolair, or US-licensed Xolair) and who had at least one post-treatment PK result with a concentration above the lower limit of quantification for omalizumab. Subjects were analysed according to the treatment they actually received. If any subject was found to be noncompliant with respect to dosing, a determination of the PK Set was made on a case-by-case basis at the blinded data review meeting (DRM) before unblinding.

Pharmacodynamic Set: The PD Set was defined as all subjects who received a complete dose of study drug (CT-P39, EU-approved Xolair, or US-licensed Xolair) and who had at least one post-treatment free IgE or total IgE concentration above the lower limit of quantification. Subjects were analysed according to the treatment they actually received.

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

Outliers: Outliers that were detected during the review of the data were discussed during the DRM. One sample (PK concentration on Day 57 of one subject in the CT-P39 treatment group of Part 1) showed sharp single-point-rise at the terminal phase, and it was captured as C_{max} of the subject. The sample was considered as outlier as it showed implausibly higher concentration compared to the values of right before and next time points, and also showed a value deviating from the expected time point of maximum concentration. In addition to the main analyses including outlier, sensitivity analyses were conducted excluding outlier to ensure robustness of study conclusions.

Statistical analysis for pharmacokinetic data

The similarity of PK for each comparison, CT-P39 *versus* EU-approved Xolair, CT-P39 *versus* US-licensed Xolair, and EU-approved Xolair *versus* US-licensed Xolair, was concluded if all 90% CIs of the ratios of geometric means were entirely contained within 80% to 125% for $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max} for Part 2.

Analysis of pharmacodynamics data

All PD analyses were performed on the PD Set unless otherwise specified. The data for each part was analysed and presented separately. Serum concentration data of free IgE and total IgE were listed by subject for the Safety Set including actual sampling times relative to dosing. Serum concentrations of free IgE and total IgE were summarized for the PD Set by treatment and time point, using descriptive statistics (number of subjects, arithmetic mean, SD, CV%, geometric mean, minimum, median, and maximum).

Free IgE concentrations that are BLQ (<6.25 ng/mL) were treated as lower limit of quantification (6.25 ng/mL) and above upper limit of quantification values (ULoQ) (>400 ng/mL) were treated as ULoQ (400 ng/mL). Total IgE concentrations that were BLQ (<2 IU/mL) were set to zero. Free and total IgE level were presented using the unit, IU/mL. If raw concentration values were not reported in this unit, the values were converted to the unit, IU/mL considering that 1.0 IU/mL IgE corresponds to 2.42 ng/mL IgE.

The individual plot, mean (±SD) plot, and overlay plot of individual serum concentration versus time profiles for free and total IgE were presented graphically on both linear and semi-logarithmic scales by treatment. For ease of presentation, actual and scheduled sampling times were used to present results for individual and mean figures respectively.

Pharmacokinetic Results

Subject Disposition

A total of 146 subjects were randomly assigned to a treatment group for Part 2 (47, 49, and 50 subjects to CT-P39, EU-approved Xolair, and US-licensed Xolair groups respectively). All 146 of the randomized subjects were administered study drug, and 142 (97.3%). Four (2.7%) subjects discontinued after study drug administration: 1 (0.7%) subject who was lost to follow-up (1 subject in the US-licensed Xolair group), 2 (1.4%) subjects due to withdrawal by subject (1 and 1 subject each in the CT-P39 and EU-approved Xolair groups), and 1 (0.7%) subject with the reason listed as other (1 subject in the EU-approved Xolair group).

Conduct of the study

There were 3 protocol amendments, and all were instituted before the first subject was randomised.

Among the enrolled subjects, two subjects in Part 2 were identified as to have failed to meet the inclusion or exclusion criteria. One subject in the CT-P39 group weighed over 90 kg at screening and Day -1 and the other subject in the CT-P39 group had taken prohibited medication (SM33 topical gel for gingival pain) within 7 days prior to study drug administration. The Applicant states that the deviations do not have a significant impact on PK results and therefore the data sets were included in the PK analysis.

Baseline Data

For Part 2 subjects, demographics and baseline characteristics were generally similar across the 3 treatment groups. In the ITT Set of Part 2, 61 (41.8%) subjects were male and 85 (58.2%) subjects were female. Most were white (114 [78.1%] subjects) and not Hispanic or Latino (118 [80.8%] subjects). Subjects ranged in age from 18 to 55 years with an overall median age of 26.5 years. The overall mean BMI at screening was 23.60 kg/m2.

Serum total IgE at screening was 34.2 IU/mL overall and the majority of subjects fell <40 IU/mL IgE (64.4%). However, the percentage of subjects with ≥40 IU/mL IgE was higher in the CT-P39 arm (40.4%) than the EU-approved Xolair (32.7%) and the US-licensed Xolair (34%).

Small differences between groups with regards medical history and concurrent disease have been noted but overall, these differences are not considered important. There were a number of subjects in each of the CT-P39 (7, 14.9%), EU-approved Xolair (8, 16.3%) and US-licensed Xolair (8, 16.0%) reported to have a medical history of an immune system disorder.

Outcomes and estimation

<u>Omalizumab serum concentrations</u>

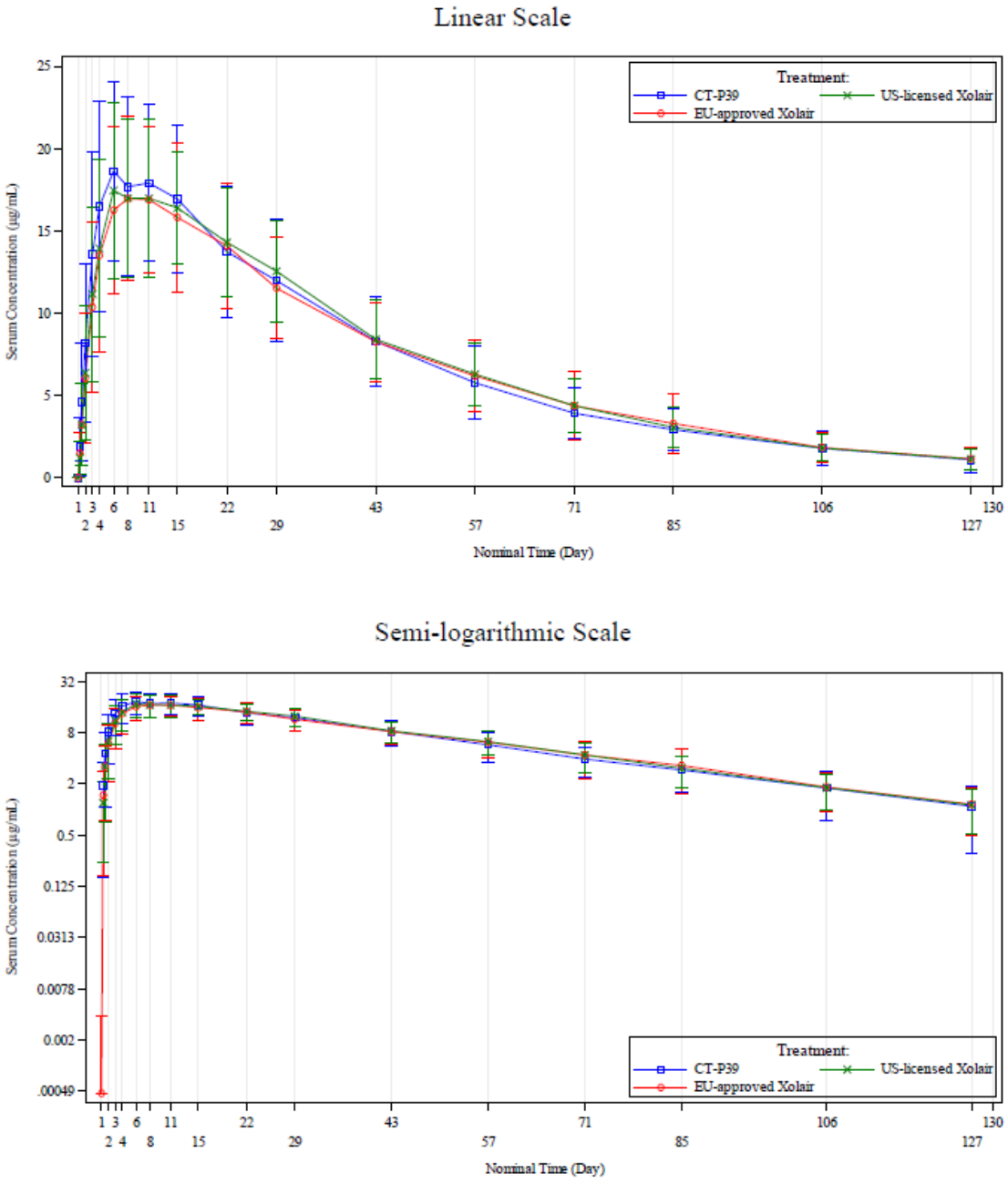


Figure 2. Mean (±SD) Serum Concentrations of Omalizumab by treatment (linear and semi logarithmic scales) – Part 2 (PK set)

Following a single SC dose of 150 mg omalizumab, the mean serum omalizumab concentration-time profiles for CT-P39, EU-approved Xolair and US-licensed Xolair were overall similar. However, omalizumab concentrations with CT-P39 were higher compared to EU-approved Xolair at the earlier time-points, approximately up to Day 15. The same trend was not strictly observed when looking at the individual PK concentration-time profiles; the concentration-time curves were generally similar, with a number of subjects showing higher concentrations at the earlier time-points in the CT-P39 group compared to the EU-approved Xolair group.

Serum omalizumab primary pharmacokinetic parameters

Table 3: Primary Pharmacokinetic Parameters of Omalizumab by Treatment group - Part 2 (PK set)

	CT-P39 (N=47)	EU-approved Xolair (N=49)	US-licensed Xolair (N=50)
$AUC_{0\text{-last}}$ (day·µg/mL)			
n	47	49	50
Mean (SD)	846.0 (251.87)	843.8 (248.04)	850.0 (213.13)
CV%	29.77	29.39	25.08
Geometric mean	808.8	807.3	822.4
Median	784.5	853.9	825.8
Minimum, Maximum	402, 1400	277, 1573	376, 1349
$AUC_{0\text{-inf}}$ (day·µg/mL)			
n	46	49	50
Mean (SD)	910.9 (278.57)	897.7 (270.25)	926.3 (273.30)
CV%	30.58	30.10	29.51
Geometric mean	868.0	856.6	888.5
Median	860.6	895.1	878.6
Minimum, Maximum	405, 1482	279, 1604	386, 1927
C_{max} (µg/mL)			
n	47	49	50
Mean (SD)	20.08 (5.9940)	18.24 (4.9981)	19.43 (5.4159)
CV%	29.849	27.398	27.874
Geometric mean	19.26	17.55	18.67
Median	19.80	17.80	19.35
Minimum, Maximum	10.5, 36.8	9.78, 29.9	9.19, 36.0

Abbreviations: $AUC_{0\text{-last}}$, Area under the concentration-time curve from time zero to the last measurable concentration; $AUC_{0\text{-inf}}$, Area under the concentration-time curve from time zero to infinity (extrapolated); C_{max}, Maximum observed concentration; CV%, percent of coefficient of variation; EU, European Union; PK, pharmacokinetic(s); US, United States.

The geometric mean for the C_{max} in the CT-P39 group (19.26 µg/mL) was higher than in the EU-approved Xolair group (17.55 µg/mL). A similar trend was seen for the geometric means for the $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$; both $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ were slightly higher in the CT-P39 group ($AUC_{0\text{-last}}$: 808.8 day·µg/mL; $AUC_{0\text{-inf}}$: 868.0 day·µg/mL) compared to the EU-approved Xolair ($AUC_{0\text{-last}}$: 807.3 day·µg/mL; $AUC_{0\text{-inf}}$: 856.6 day·µg/mL). In general, the C_{max} (19.43 µg/mL), $AUC_{0\text{-last}}$ (850.0 day·µg/mL), and $AUC_{0\text{-inf}}$ (926.3 day·µg/mL) for US-licensed Xolair group was also similar to the test and reference groups.

Serum omalizumab secondary pharmacokinetic parameters

Table 4: Secondary Pharmacokinetic Parameters of Omalizumab - Part 2 (PK set)

Parameter (unit)	CT-P39 (N=47)	EU-approved Xolair (N=49)	US-licensed Xolair (N=50)
T_{max} (day)			
n	47	49	50
Mean (SD)	7.145 (3.2898)	8.821 (3.3972)	7.999 (3.7898)
CV%	46.0417	38.5117	47.3762
Geometric mean	6.370	8.214	7.155
Median	7.098	7.306	7.183
Minimum, Maximum	2.00, 14.26	3.00, 18.26	3.00, 21.17
$t_{1/2}$ (day)			
n	46	49	50
Mean (SD)	29.30 (9.5158)	27.69 (5.5603)	28.63 (6.6290)
CV%	32.477	20.081	23.151
Geometric mean	28.16	27.10	27.96
Median	28.42	26.93	28.04
Minimum, Maximum	17.0, 66.4	14.3, 39.5	16.9, 56.7
λ_z (1/day)			
n	46	49	50
Mean (SD)	0.02543 (0.0062273)	0.02619 (0.0061733)	0.02536 (0.0054466)
CV%	24.485	23.571	21.479
Geometric mean	0.02461	0.02557	0.02479
Median	0.02439	0.02574	0.02472
Minimum, Maximum	0.0104, 0.0407	0.0176, 0.0485	0.0122, 0.0410
CL/F (L/day)			
n	46	49	50
Mean (SD)	0.1820 (0.062043)	0.1850 (0.071201)	0.1764 (0.056007)
CV%	34.094	38.490	31.757
Geometric mean	0.1728	0.1751	0.1688
Median	0.1743	0.1676	0.1708
Minimum, Maximum	0.101, 0.370	0.0935, 0.538	0.0778, 0.389
V_z/F (L)			
n	46	49	50
Mean (SD)	7.258 (1.9122)	7.172 (2.1764)	7.011 (1.8079)
CV%	26.344	30.344	25.785
Geometric mean	7.021	6.848	6.810
Median	6.603	6.453	6.599
Minimum, Maximum	4.31, 11.8	2.13, 13.7	4.56, 13.4
$\%AUC_{ext}$ (%)			
n	46	49	50
Mean (SD)	5.513 (5.4293)	5.669 (3.7830)	6.519 (9.6422)
CV%	98.486	66.727	147.90
Geometric mean	4.142	4.508	4.711
Median	4.441	5.566	4.757
Minimum, Maximum	0.733, 35.3	0.370, 22.8	0.659, 70.5

Abbreviations: $\%AUC_{ext}$, area under the concentration-time curve extrapolated from time zero to infinity as a percentage of total area under the concentration-time curve; CL/F, apparent clearance after subcutaneous dosing; V_z/F, apparent volume of distribution during the terminal phase; EU, European Union; CV%, percent of coefficient of variation; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; λ_z, terminal elimination rate constant; T_{max}, time to maximum serum concentration; US, United States.

The median T_{max} was approximately 7 days in all 3 treatment groups. The CV% for t_{max} was moderate across groups (38.5% to 47.4%), with values ranging from 2 to 14 days for CT-P39 and 3 to 18 days for EU-approved Xolair. The geometric mean terminal half-life ($t_{1/2}$) in the CT-P39 group (28.16 days) was longer than in the EU-approved Xolair group (27.10 days).

Overall, the secondary pharmacokinetic parameters for the US-licensed Xolair were similar the CT-P39 and EU-approved Xolair results.

Statistical Analysis of Pharmacokinetic Similarity

Table 5: Statistical Analysis of Primary Pharmacokinetic Parameters of Omalizumab - Part 2 (PK set)

PK Parameter (units)	Geometric LSM						CT-P39 /EU-approved Xolair	CT-P39 /US-licensed Xolair	EU-approved Xolair /US-licensed Xolair
	CT-P39 (N=47)		EU-approved Xolair (N=49)		US-licensed Xolair (N=50)				
	n	Results	n	Results	n	Results	Ratio[a] [90% CI[b]]	Ratio[a] [90% CI[b]]	Ratio[a] [90% CI[b]]
$AUC_{0\text{-last}}$ (day·µg/mL)	47	832.06	49	800.07	50	837.92	104.00 [94.96 - 113.89]	99.30 [90.79 - 108.61]	95.48 [87.36 - 104.37]
$AUC_{0\text{-inf}}$ (day·µg/mL)	46	897.81	49	850.05	50	909.42	105.62 [95.91 - 116.31]	98.72 [89.76 - 108.58]	93.47 [85.09 - 102.68]
C_{max} (µg/mL)	47	19.73	49	17.44	50	18.99	113.14 [103.15 - 124.11]	103.88 [94.83 - 113.80]	91.82 [83.87 - 100.52]

Abbreviations: ANCOVA, analysis of covariance; $AUC_{0\text{-last}}$, area under the concentration-time curve from time zero to the last measurable concentration; $AUC_{0\text{-inf}}$, area under the concentration-time curve from time zero to infinity (extrapolated); CI, confidence interval; C_{max}, maximum observed concentration; EU, European Union; IgE, immunoglobulin E; LSM, least square mean; PK, pharmacokinetic(s); US, United States.

Note: An ANCOVA is performed with the natural log-transformed PK parameters as the dependent variable, treatment as a fixed effect and baseline body weight, total IgE level, and sex as covariates.

[a] Calculated using least-squares means according to the formula: exp(DIFFERENCE) × 100.

[b] 90% Geometric Confidence Interval calculated according to the formula: $\exp(\text{DIFFERENCE} \pm t_{(df\text{Residual})} \times SE_{\text{DIFFERENCE}}) \times 100$.

For the primary endpoints of $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$, for CT-P39 vs EU-approved Xolair, the geometric mean ratios (GMR), and the 90% CIs were within the 80-125% acceptance criteria. For $AUC_{0\text{-last}}$ the GMR was 104.00% with 90% CI of 94.96 – 113.89%, and for $AUC_{0\text{-inf}}$ the GMR was 105.62% with 90% CI of 95.91 – 116.31%. Both $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ included the 100% and are acceptable to show biosimilarity.

For the primary endpoint of C_{max}, for CT-P39 vs EU-approved Xolair, the GMRs and 90% CIs were within the 80-125% acceptance criteria. However, although the point estimate for GMR was 113.14%, the 90% CI ranged 103.15 – 124.11%. The upper bound of the CI was very close to the 125% limit for the acceptance criteria, and unity was not included in the 90% CI, suggesting that the C_{max} was substantially higher with the test CT-P39 than the reference EU-approved Xolair.

Ancillary Analyses

No subgroup analyses were planned or performed for this study CT-P39 1.1. The incidence of post-treatment ADA was lower in CT-P39 group (1, 2.1%) than the EU-approved Xolair group (13, 26.5%). NAb was not detected in the CT-P39 group and was detected in 1 subject in the EU-approved Xolair group. There was no subject with an increasing trend in ADA titre after treatment, and the majority had low ADA titre. Although there was a generally low incidence of ADA and NAb in this study, there was a difference between the incidence in CT-P39 and EU-approved Xolair.

Part 1 of Study CT-P39 1.1 was not required for the MAA in the EU as outlined in the SA received by the applicant in October 2019 (EMEA/H/SA/4063/1/FU/1/2019/III). The Applicant has presented the results of Part 1 as part of the CSR CT-P39 1.1 but has presented them separately as part of the report.

Study CT-P39 1.1 – Part 1

Following a single SC administration of CT-P39 or EU-approved Xolair, the mean serum concentrations of omalizumab at each timepoint up to Day 127 were generally comparable to Part 2. The values for the PK parameters in Part 1 were overall similar to the values for the PK parameters in Part 2. Part 1 showed the same trend seen in Part 2 where the means and for C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were higher in the CT-P39 group than the EU-approved Xolair group. For example, the mean C_{max} in for CT-

P39 Part 1 (20.29 µg/mL) and Part 2 (20.08 µg/mL) were higher than the mean for EU-approved Xolair in Part 1 (17.69 µg/mL) and Part 2 (18.24 µg/mL) respectively. The other secondary PK parameters investigated in both Part 1 and Part 2 were overall similar.

Post-hoc analyses

Study CT-P39 1.1 – PK parameters by batch and protein content normalisation

In Study CT-P39 1.1, two batches of EU-approved Xolair (AVXS234905 and AVXS241303) were used whereas for CT-P39 and US-licensed Xolair, only one batch was used. For EU-approved Xolair, two batches were used because the duration of subject enrolment took longer than expected. Therefore, the expiry date of the first batch of EU-approved Xolair had passed before all subjects were enrolled and administered with drug, so another batch of EU-approved Xolair was purchased.

As shown in the table below, there are differences in the primary PK parameters among different batches of EU-approved Xolair. Considering that the protein contents of the two batches were similar, and that the mean ± SD ranges of the two batches overlap, the differences in PK parameters are not considered clinically meaningful. Since the number of subjects who received EU-approved Xolair batch AVXS241303 is small, cautious interpretation is needed.

Table 6: Descriptive Statistics of Primary PK Parameters of Omalizumab by Batch in Study CT-P39 1.1: PK Set

Treatment Group		CT-P39 (N=47)	EU-approved Xolair (N=49)		US-licensed Xolair (N=50)
Batch Number		CTP39CLN2	AVXS234905	AVXS241303	3316571
$AUC_{0\text{-}inf}$ (day·µg/mL)	n	46	43	6	50
	Mean ± SD	910.9 ± 278.57	873.4 ± 272.30	1071.9 ± 191.94	926.3± 273.30
	CV%	30.58	31.18	17.91	29.51
	GM	868.0	831.7	1058.0	888.5
	Median	860.6	850.8	1037.3	878.6
	Min, Max	405, 1482	279, 1604	855, 1360	386, 1927
$AUC_{0\text{-}last}$ (day·µg/mL)	n	47	43	6	50
	Mean ± SD	846.0 ± 251.87	821.4 ± 248.95	1004.5 ± 186.34	850.0 ± 213.13
	CV%	29.77	30.31	18.55	25.08
	GM	808.8	784.6	990.2	822.4
	Median	784.5	792.6	973.2	825.8
	Min, Max	402, 1400	277, 1573	765, 1284	376, 1349
C_{max} (µg/mL)	n	47	43	6	50
	Mean ± SD	20.08 ± 5.9940	17.74 ± 4.8870	21.82 ± 4.6619	19.43 ± 5.4159
	CV%	29.849	27.542	21.369	27.874
	GM	19.26	17.07	21.36	18.67
	Median	19.80	17.60	23.10	19.35
	Min, Max	10.50, 36.80	9.78, 29.90	14.70, 26.30	9.19, 36.00

Abbreviations: CV%, Percent coefficient of variation; GM, Geometric mean; N, number of subjects in the PK Set; n, number of subjects who contributed to summary statistics; PK, pharmacokinetic(s); SD, Standard deviation

To further assess the potential impact of the different protein content among batches on the PK data analysis, analyses of primary PK endpoints of Study CT-P39 1.1 were performed by adjusting PK parameters based on the protein content of each batch used for individual subjects (Table 7). The protein-adjusted results of primary PK endpoints were still completely retained within the pre-defined equivalence margin of 80-125% including unity in all comparisons.

In conclusion, because the result of protein-adjusted PK analysis still supported PK equivalence among CT-P39, EU-approved Xolair and US-licensed Xolair, the applicant believes that the difference in

batches used in the EU-approved Xolair group did not have meaningful impact on the clinical outcomes of the study.

Table 7: Statistical Analysis of Protein-adjusted Primary PK Parameters of Omalizumab in Study CT-P39 1.1: PK Set

PK Parameter (unit)	Geometric LS Mean			Ratio (%) of Geometric LS Means (90% CI)	
	Treatment	n	Results	Treatment Comparison	Results
AUC_{0-inf} (day·µg/mL)	CT-P39	46	5.76	CT-P39 vs. EU-approved Xolair	99.29 (90.15-109.35)
	EU-approved Xolair	49	5.80	CT-P39 vs. US-licensed Xolair	93.53 (85.03-102.87)
	US-licensed Xolair	50	6.16	EU-approved Xolair vs. US-licensed Xolair	94.20 (85.74-103.49)
AUC_{0-last} (day·µg/mL)	CT-P39	47	5.34	CT-P39 vs. EU-approved Xolair	97.76 (89.26-107.07)
	EU-approved Xolair	49	5.46	CT-P39 vs. US-licensed Xolair	94.08 (86.01-102.90)
	US-licensed Xolair	50	5.68	EU-approved Xolair vs. US-licensed Xolair	96.23 (88.03-105.19)
C_{max} (µg/mL)	CT-P39	47	0.13	CT-P39 vs. EU-approved Xolair	106.36 (96.96-116.68)
	EU-approved Xolair	49	0.12	CT-P39 vs. US-licensed Xolair	98.42 (89.83-107.82)
	US-licensed Xolair	50	0.13	EU-approved Xolair vs. US-licensed Xolair	92.53 (84.52-101.31)

Note: An ANCOVA is performed with the natural log-transformed PK parameters as the dependent variable, treatment as a fixed effect and baseline body weight, total IgE level, and sex as covariates. PK parameter results of each individual have been divided by the protein content.
Abbreviations: CI, confidence interval; LS, least square; n, number of subjects who contributed to summary statistics, PK, pharmacokinetic(s)

Study CT-P39 1.1 – PK parameters by baseline total IgE stratification

For primary PK analysis, ANCOVA has been performed with the natural log-transformed PK parameters as the dependent variable, treatment as a fixed effect and baseline body weight, total IgE level, and sex as covariates. In ANCOVA model, numeric value of total IgE level at screening was used instead of category variable at stratification. The total IgE are not significant (p-value >0.05) in ANCOVA model and this could be interpreted that difference in total IgE over subjects have no significant effect on PK parameters.

The Applicant has also conducted additional post-hoc analysis to descriptively compare PK outcomes in two different total screening IgE subgroups (≥40 IU/mL or <40 IU/mL) (Table 8). Considering the mechanism of action of omalizumab, the lower the screening total IgE level, the higher the total PK concentration is expected. However, the data analysed by screening total IgE at a threshold of 40 IU/mL did not show a consistent trend among the treatment groups. Consequently, the applicant concluded that there was no meaningful impact of the subjects' screening total IgE levels on the PK outcomes.

Table 8: Descriptive Statistics of Primary Pharmacokinetic Parameters by Screening Total IgE Subgroup – Part 2 (PK Set)

	Screening Total IgE ≥ 40IU/mL			Screening Total IgE < 40IU/mL		
Parameters Statistics	**CT-P39**	**EU-approved Xolair**	**US-licensed Xolair**	**CT-P39**	**EU-approved Xolair**	**US-licensed Xolair**
$AUC_{0\text{-}inf}$						
n	18	16	17	28	33	33
mean (SD)	801.0 (189.28)	922.0 (363.04)	898.6 (177.41)	981.6 (305.85)	886.0 (217.57)	940.5 (313.09)
$AUC_{0\text{-}last}$						
n	19	16	17	28	33	33
mean (SD)	746.2 (177.94)	880.3 (335.49)	856.8 (162.82)	913.7 (274.24)	826.1 (196.32)	846.4 (237.20)
C_{max}						
n	19	16	17	28	33	33
mean (SD)	18.026 (4.4070)	19.025 (5.6737)	18.565 (2.6457)	21.475 (6.5785)	17.863 (4.6826)	19.875 (6.3885)

Abbreviations: $AUC_{0\text{-}last}$, area under the concentration-time curve from time zero to the last quantifiable concentration; $AUC_{0\text{-}inf}$, area under the concentration-time curve from time zero to infinity; C_{max}, maximum serum concentration; EU, European Union; IgE, Immunoglobulin E; SD, standard deviation; PK, pharmacokinetic(s); US, United States.

Study CT-P39 1.1 – PK parameters by presence of medical history of immune system disorder

To investigate whether there was an effect of a history of an immune system disorder on the results of the study, a descriptive analysis of the PK parameters of Study CT-P39 1.1 Part 2 was performed for subgroups of subjects by presence of a medical history of immune system disorders. The analysis results showed a slightly lower area under the concentration-time curve (AUC) in the subjects who had a history of immune system disorder in the CT-P39 and EU-approved Xolair groups while similar PK were observed in US-licensed Xolair group, but given the large variability of the data and the small number of subjects with medical history of immune system disorder, the effect on PK should be considered with caution (Table 9).

Table 9: Summary of Pharmacokinetic Parameters by Presence of Medical History of Immune System Disorder in Study CT-P39 1.1 – Part 2: PK set

	CT-P39 (N=47)		EU-approved Xolair (N=49)		US-licensed Xolair (N=50)	
Presence of MH of Immune system disorder	**With MH (n=7)**	**Without MH (n=40)**	**With MH (n=8)**	**Without MH (n=41)**	**With MH (n=8)**	**Without MH (n=42)**
PK Parameter (units)						
$AUC_{0\text{-}last}$, n	7	40	8	41	8	42
Mean (SD) (day*µg/mL)	755.2 (204.04)	861.8 (258.23)	731.4 (191.82)	865.8 (253.71)	863.6 (185.45)	847.4 (219.94)
$AUC_{0\text{-}inf}$, n	7	39	8	41	8	42
Mean (SD) (day*µg/mL)	784.9 (225.78)	933.5 (283.54)	764.8 (208.67)	923.7 (275.31)	902.6 (207.98)	930.8 (285.93)
C_{max}, n	7	40	8	41	8	42
Mean (SD) (µg/mL)	20.69 (8.02)	19.98 (5.69)	16.34 (5.25)	18.61 (4.93)	19.18 (3.63)	19.48 (5.73)

Abbreviations: $AUC_{0\text{-}last}$, Area under the concentration-time curve from time zero to the last measurable concentration; $AUC_{0\text{-}inf}$, Area under the concentration-time curve from time zero to infinity (extrapolated); C_{max},

	CT-P39 (N=47)		EU-approved Xolair (N=49)		US-licensed Xolair (N=50)	
Presence of MH of Immune system disorder	With MH (n=7)	Without MH (n=40)	With MH (n=8)	Without MH (n=41)	With MH (n=8)	Without MH (n=42)

Maximum serum concentration; MH, Medical history; n, Number of subjects; N, Total number of subjects; PK, Pharmacokinetic; SD, Standard deviation

Study CT-P39 3.1

Methods

CT-P39 3.1 was a double-blind, randomized, active-controlled, parallel group, multi-centre, Phase 3 study to evaluate the efficacy and safety of CT-P39 compared with EU-approved Xolair, when SC administered as an add-on therapy for the treatment of patients with CSU who remain symptomatic despite an approved dose of nonsedating H1-antihistamine treatment.

Approximately 600 male and female patients with CSU, aged between 12 and 75 years (both inclusive), were planned to be enrolled and randomized to 300 mg of CT-P39, 300 mg of Xolair, 150 mg of CT-P39, and 150 mg of Xolair in a 2:2:1:1 ratio in Treatment Period I. All patients who completed Treatment Period I underwent the second randomization process prior to the study drug administration at Week 12 and entered Treatment Period II. Patients who were initially randomized to 300 mg of Xolair (Arm 2) in Treatment Period I were re-randomized in a ratio of 1:1 to switching arm (Arm 2-1) or non-switching arm (Arm 2-2). Patients in Arms 3 and 4 were changed from 150 mg of CT-P39 or EU-approved Xolair, to 300 mg of CT-P39 or EU-approved Xolair respectively.

A secondary objective of CT-P39 3.1 was to assess and compare the C_{trough} of omalizumab between CT-P39 and EU-approved Xolair treatment groups following 150 or 300 mg dose administrations in patients with CSU. The blood samples for PK analysis of omalizumab were drawn at Weeks 0, 4, 8, 12, 16, 20, 24 and EOS (Week 40). For study drug administration visits, the samples were drawn prior to the study drug administration.

Pharmacokinetic Results

Table 10: Mean (SD) Through serum concentration (µg/mL) of Omalizumab (Pharmacokinetic Set) - Treatment Period I

Visit	Statistics	Arm 1 (N = 199)	Arm 2 (N = 204)	Arm 3 (N = 105)	Arm 4 (N = 102)
Week 4 (predose)	n	196	201	105	101
	Mean (SD)	18.3427 (6.6702)	19.5661 (8.0147)	8.6017 (3.8047)	10.4523 (6.6250)
Week 8 (predose)	n	191	195	103	100
	Mean (SD)	26.8233 (9.7057)	27.7412 (11.5178)	13.1061 (5.1159)	13.7333 (6.2829)
Week 12 (predose)	n	187	193	101	97
	Mean (SD)	31.5079 (12.1197)	31.3568 (13.4433)	14.6747 (6.3159)	15.8001 (7.6567)

Abbreviations: Arm 1 = CT-P39 300 mg; Arm 2 = Xolair 300 mg; Arm 3 = CT-P39 150 mg; Arm 4 = Xolair 150 mg; n = Number of patients; N = Total number of patients; SD = Standard deviation.

Note: Below lower limit of quantification was treated as zero (0).

During Treatment Period I, the mean C_{trough} of omalizumab was similar between CT-P39 300 mg and Xolair 300 mg treatment arms (Arm 1 and 2) and between CT-P39 150 mg and Xolair 150 mg treatment arms (Arm 3 and 4). The mean C_{trough} of CT-P39 300 mg and Xolair 300 mg treatment arms (Arm 1 and 2) were higher compared to the mean C_{trough} of CT-P39 150 mg and Xolair 150 mg treatment arms (Arm 3 and 4), resulting from the given dose level difference.

Table 11: Mean (SD) Through serum concentration (µg/mL) of Omalizumab (PK – TP2 Subset) - Treatment Period II

Visit	Statistics	Arm 1 (N = 185)	Arm 2-1 (N = 95)	Arm 2-2 (N = 95)	Arm 3 (N = 100)	Arm 4 (N = 96)
Week 16 (predose)	n	183	95	94	98	95
	Mean (SD)	33.2718 (13.4148)	35.3776 (16.5145)	32.6859 (12.5492)	24.4849 (9.9810)	26.9629 (10.9915)
Week 20 (predose)	n	181	93	93	99	94
	Mean (SD)	34.6532 (13.6460)	35.9274 (17.1806)	33.5548 (13.0928)	28.5571 (11.5258)	31.9396 (12.6032)
Week 24	n	177	92	94	97	92
	Mean (SD)	35.4310 (14.9890)	35.8710 (18.0929)	33.5061 (14.2554)	30.4152 (13.1669)	33.6363 (16.5509)

Abbreviations: Arm 1 = CT-P39 300 mg Maintenance; Arm 2-1 = Switched from Xolair to CT-P39 300 mg after Week 12; Arm 2-2 = Xolair 300 mg Maintenance; Arm 3 = Dose increased from CT-P39 150 mg to 300 mg after Week 12; Arm 4 = Dose increased from Xolair 150 mg to 300 mg after Week 12; n = Number of patients; N = Total number of patients; PK = Pharmacokinetic; SD = Standard deviation; TP2 = Treatment Period II.

Note: Below lower limit of quantification was treated as zero (0).

The mean C_{trough} of omalizumab observed during Treatment Period II was similar among Arm 1, Arm 2-1, and Arm 2-2, which indicated that PK profiles after a single transition from Xolair to CT-P39, were not different from those of patients maintained on CT-P39 or Xolair. During Treatment Period II, C_{trough} of omalizumab increased up to 2-fold in both Arm 3 and Arm 4 when the dose was doubled. At Week 24, the mean C_{trough} of omalizumab was similar between all 5 treatment arms.

Arm 2-1, which assessed the switch from EU-approved Xolair to CT-P39, saw a larger increase in C_{trough} between Week 12 (31.5079 µg/mL) and Week 16 (35.3776 µg/mL) than both Arm 1 and Arm 2-2. This increase was maintained up to Week 24 indicating steady state had been achieved. Arm 2-2 did not see the same large increase between Week 12 (31.3568 µg/mL) and Week 16 (32.6859 µg/mL) and in general, was slightly lower at all time-points in Treatment Period II than either Arm 1 or Arm 2-1. In Arm 1, Arm 2-1, and Arm 2-2 there was a general trend of an increase in mean C_{trough} between Week 12 and 16, however this increase was notably larger in Arm 2-1 which is the treatment arm designed to show if there is any effect when switching from EU-approved Xolair to CT-P39.

To investigate the extent of increase between Week 12 and Week 16 for Arm 1, Arm 2-1, and Arm 2-2, the trough serum concentrations of omalizumab from Week 4 up to Week 16 are presented for the PK-TP2 Subset **(Figure 3** and **Table 12**).

As shown below, C_{trough} in Arm 2-1 (yellow line) was slightly higher compared with Arm 1 (blue line) and Arm 2-2 (purple line) since Week 4. This tendency was maintained even after single transition at Week 12 from EU-approved Xolair to CT-P39 for the patients in Arm 2-1. Considering that same treatment was given in Arm 2-1 and Arm 2-2 during the first 12 weeks, the difference of C_{trough} between the two groups did not result from treatment difference. Given the numerical difference observed between Arm 2-1 and Arm 2-2 at an earlier time point, the increase in mean C_{trough} after

switching treatment between Week 12 and Week 16 in Arm 2-1 (increase: 2.74 µg/mL) compared to Arm 2-2 (increase: 2.40 µg/mL) can be considered to be at a comparable level.

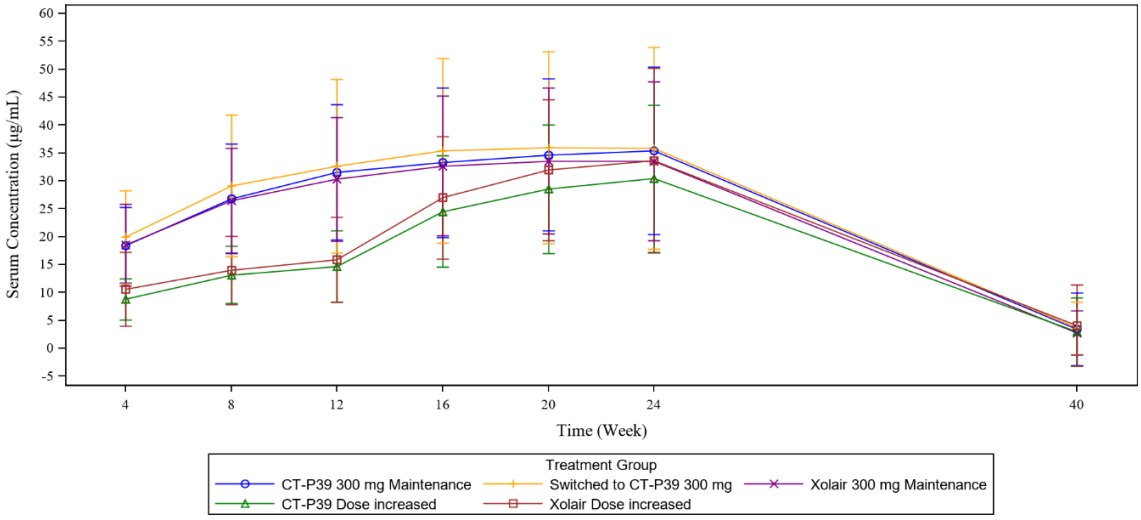


Figure 3. Mean (±SD) Trough Serum Concentration of Omalizumab versus Time by Treatment in Study CT-P39 3.1: PK-TP2 Subset

Table 12: Descriptive Statistics of Trough Serum Concentration (µg/mL) up to Week 16 (Predose) in Study CT-P39 3.1: PK-TP2 Subset

Visit Statistics	**Arm 1** **(N=185)**	**Arm 2-1** **(N=95)**	**Arm 2-2** **(N=95)**
Week 4 (Predose)			
n	184	95	94
mean (SD)	18.4366 (6.7941)	19.9368 (8.3451)	18.4754 (7.3395)
median	18.7000	19.7000	18.4000
range	0.000 - 42.500	0.000 - 46.100	0.000 - 49.800
Week 8 (Predose)			
n	184	95	94
mean (SD)	26.8519 (9.7482)	29.0937 (12.6922)	26.4184 (9.4230)
median	26.6000	28.4000	26.6000
range	1.350 - 56.200	0.000 - 59.900	7.480 - 52.100
Week 12 (Predose)			
n	184	94	95
mean (SD)	31.5532 (12.1071)	32.6340 (15.5652)	30.2848 (11.1099)
median	31.4000	30.9000	30.2000
range	5.190 - 67.100	6.440 - 85.000	8.720 - 59.600
Week 16 (Predose)*			
n	183	95	94
mean (SD)	33.2718 (13.4148)	35.3776 (16.5145)	32.6859 (12.5492)
median	33.1000	34.1000	31.2000
range	0.127-75.300	3.400 - 77.200	8.120 - 68.600

*C_{trough} at Week 16 (Predose) is collected after single transition on Week 12 visit

Visit Statistics	Arm 1 (N=185)	Arm 2-1 (N=95)	Arm 2-2 (N=95)

Abbreviations: Arm 1, CT-P39 300 mg Maintenance; Arm 2-1, Switched from EU-approved Xolair to CT-P39 300 mg after Week 12; Arm 2-2, EU-approved Xolair 300 mg Maintenance; n, Number of patients; N, Total number of patients; PK, Pharmacokinetic; SD, Standard deviation; TP2, Treatment Period II

2.6.2.2. Pharmacodynamics

Study CT-P39 1.1

A secondary objective for Study CT-P39 1.1 was to assess the pharmacodynamic similarity of CT-P39, EU-approved Xolair, and US-licensed Xolair. All PD analyses were performed on the PD Set unless otherwise specified. Two subjects, 1 subject each of CT-P39 and US-licensed Xolair groups, who showed BLQ values at all time points in both of total and free IgE results were excluded from the PD Set of Part 2.

The pharmacodynamic endpoints for this study were:

Free IgE:

- Minimum serum concentration (Cmin)
- Time to Cmin (Tmin)
- Maximum percentage decrease in serum free IgE concentration from baseline (max % decrease)

Total IgE:

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

Pharmacodynamic Results

For the secondary PD endpoints of free IgE, the Cmin of free IgE was similar between CT-P39 (3.5267 IU/mL) and EU-approved Xolair (3.559 IU/mL). The median Tmin of free IgE was lower for CT-P39 (3.000 days) compared with EU-approved Xolair (5.051 days). The mean maximum % decrease of free IgE from baseline was higher in CT-P39 (73.05%) compared with EU-approved Xolair (64.20%). The T_{max} of total IgE was very similar between CT-P39 (28.191 days) and EU-approved Xolair (28.156 days). The mean (SD) C_{max} of total IgE was higher in the CT-P39 group (245.2391 IU/mL, SD 223.24856) compared with the EU-approved Xolair group (174.2857 IU/mL, SD 145.17432). There was a high level of variability for the C_{max} of total IgE, with the CV% for CT-P39 group being 91% and for EU-approved Xolair being 83%. The mean maximum % increase of total IgE saw a similar outcome, with a higher mean % increase for CT-P39 (574.26%, SD 309.426) in comparison to EU-approved Xolair (494.45%, SD 235.443).

Table 13: Summary of Serum Pharmacodynamic Parameters of Omalizumab - Part 2 (PD Set)

Parameter (unit)	CT-P39 (N=46)	EU-approved Xolair (N=49)	US-licensed Xolair (N=49)
C_{min} of free IgE (IU/mL)			
n	31	38	32
Mean (SD)	3.5267 (1.45275)	3.5590 (1.56235)	3.7002 (1.69613)
CV%	41.19351	43.89798	45.83942
T_{min} of free IgE (day)			
n	31	38	32
Mean (SD)	5.138 (5.4161)	8.278 (13.3241)	5.955 (7.7122)
CV%	105.4112	160.9510	129.4985
Geometric mean	2.372	3.511	3.024
Median	3.000	5.051	3.002
Minimum, Maximum	0.25, 21.21	0.25, 70.17	0.25, 41.07
Maximum % decrease of free IgE (%)			
n	30	38	32
Mean (SD)	73.05 (21.253)	64.20 (24.924)	66.62 (24.813)
CV%	29.093	38.825	37.247
Geometric mean	69.18	54.76	58.27
Median	81.44	72.14	71.85
Minimum, Maximum	29.7, 95.5	4.3, 95.2	3.1, 93.4
C_{max} of total IgE (IU/mL)			
n	46	49	49
Mean (SD)	245.2391 (223.24856)	174.2857 (145.17432)	219.5714 (187.41287)
CV%	91.03301	83.29674	85.35394
Geometric mean	156.3357	116.3128	132.6764
Median	172.0000	131.0000	143.0000
Minimum, Maximum	3.000, 1076.000	5.000, 662.000	5.000, 641.000
T_{max} of total IgE (day)			
n	46	49	49
Mean (SD)	31.975 (15.6127)	30.160 (14.9298)	28.818 (13.6354)
CV%	48.8282	49.5024	47.3151
Geometric mean	27.683	27.186	25.991
Median	28.191	28.156	28.087
Minimum, Maximum	3.00, 70.13	14.01, 71.07	10.18, 73.07
Maximum % increase of total IgE (%)			
n	45	48	47
Mean (SD)	574.26 (309.426)	494.45 (235.443)	857.82 (2146.900)
CV%	53.883	47.617	250.274
Geometric mean	495.10	436.82	524.58
Median	523.08	473.89	500.00
Minimum, Maximum	75.6, 1720.8	58.1, 1400.0	88.5, 15166.7

Abbreviations: C_{max}, maximum observed concentration; C_{min}, minimum observed concentration; CV%, percent of coefficient of variation; EU, European Union; IgE, immunoglobulin E; T_{max}, time to maximum serum concentration; T_{min}, time to minimum serum concentration; PD, pharmacodynamic(s); US, United States.

Total IgE was a stratification factor for this study and following stratification the percentage of subjects with ≥40 IU/mL IgE at baseline was higher in the CT-P39 arm (40.4%) than the EU-approved Xolair (32.7%) and the US-licensed Xolair (34%). Differences in the maximum % decrease reflected slight variations in the baseline free IgE. However, the observed mean free IgE $C_{min,}$ the PD parameter of free IgE C_{min} is more relevant in assessing omalizumab's potential effect on PD. In the originator omalizumab study, the observed free IgE Cmin was 7.50 ng/mL to 7.90 ng/mL (approximately 3.10 to 3.26 IU/mL), which is similar to the mean free IgE C_{min} values of 3.5 to 3.7 IU/mL observed in Study CT-P39 1.1.

Table 14: Predose Serum Free IgE and Free IgE C_{min} and Maximum % Decrease in Study CT-P39 1.1 – Part 2: PD Set

Parameter (units)	CT-P39 (N=46)	EU-approved Xolair (N=49)	US-licensed Xolair (N=49)
Predose Free IgE, n	46	49	49
Mean (SD) (IU/mL)	21.9 (31.98)	13.9 (14.97)	14.4 (17.51)
Median (IU/mL)	6.901	7.190	5.702
Minimum, Maximum (IU/mL)	2.58, 165.29	2.58, 69.01	2.58, 79.75

Parameter (units)	CT-P39 (N=46)	EU-approved Xolair (N=49)	US-licensed Xolair (N=49)
Free IgE C_{min}, n	31	38	32
Mean (SD) (IU/mL)	3.5 (1.45)	3.6 (1.56)	3.7 (1.70)
Median (IU/mL)	2.583	2.583	2.583
Minimum, Maximum (IU/mL)	2.583, 8.182	2.583, 7.562	2.583, 8.058
Maximum % decrease, n	30	38	32
Mean (SD) (%)	73.05 (21.253)	64.20 (24.924)	66.62 (24.813)
Median (%)	81.44	72.14	71.85
Minimum, Maximum (%)	29.7, 95.5	4.3, 95.2	3.1, 93.4

Abbreviations: C_{min}, Minimum serum concentration; IgE, Immunoglobulin E; n, Number of subjects; N, Total number of subjects; PD, Pharmacodynamic set; SD, Standard deviation

Study CT-P39 3.1

A secondary safety endpoint for Study CT-P39 3.1 was to assess total and free serum IgE concentration throughout the treatment period with CT-P39 or EU-approved Xolair. As these parameters were measured as a safety endpoint, the serum concentrations of total and free IgE for the Safety Set and the Safety-TP2 Subset are summarized by treatment arm.

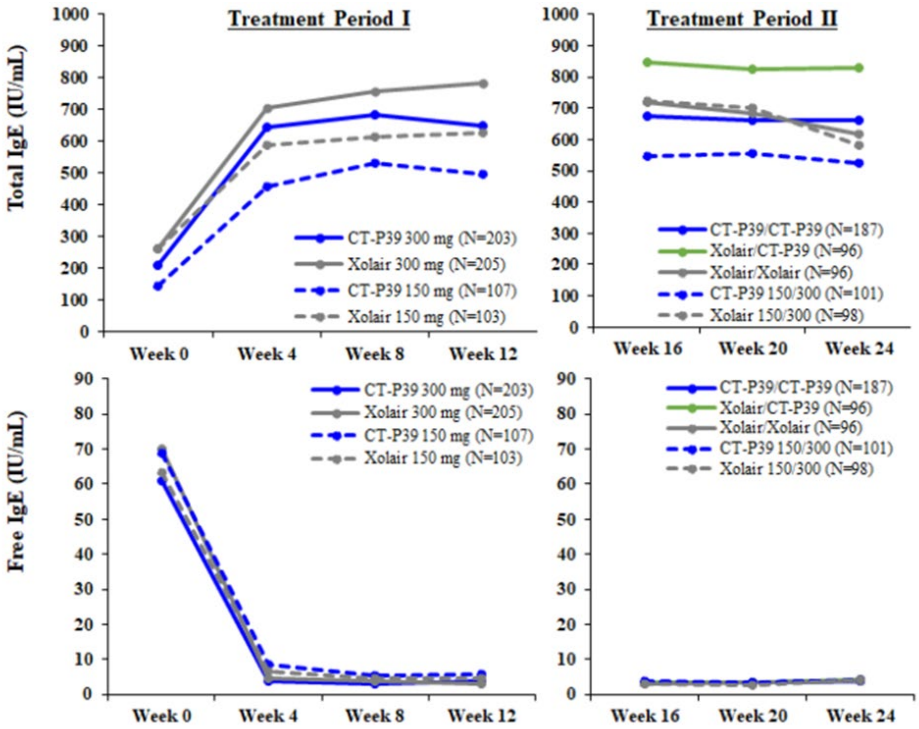


Figure 4. Mean Serum Concentrations of Total and Free IgE during Treatment Period I and Treatment Period II in Study CT-P39 3.1: Safety Set and Safety-TP2 Subset

Overall, the mean total and free serum IgE was generally comparable between the CT-P39 arms and the EU-approved Xolair arms. All groups showed an increase in mean total IgE and a suppression of

free IgE. There was an increase in mean total IgE when transitioning from EU-approved Xolair to CT-P39, however mean free IgE was not affected, indicating there was no difference between the groups.

2.6.3. Discussion on clinical pharmacology

Discussion on Pharmacokinetics

Comparative PK data of CT-P39 was generated in one PK study in healthy volunteers (CT-P39 1.1, Part 2) following a single subcutaneous (SC) injection. Additionally, secondary PK characteristics after repeat SC administration were evaluated in a phase 3 confirmatory study in patients aged between 12 and 75 years of age with a history of at least 6 months of CSU who had hives and itching for 6 consecutive weeks or more despite current use of H1-antihistamines (CT-P39 3.1). The analytical methods used during the clinical development have been suitably validated in line with the relevant guidelines.

Pivotal Pharmacokinetics Study CT-P39 1.1

CT-P39 1.1 is a Phase 1 pivotal study investigating PK similarity. This was a 2-part, randomized, double-blind, three-arm, parallel group, single-dose, active comparator study, designed to evaluate the safety, PK, PD, and immunogenicity of CT-P39 compared to those of EU-approved Xolair and US-licensed Xolair in healthy subjects. Given the long elimination half-life of omalizumab (approximately 26 days), the parallel study design is acceptable. Study follow-up to an EoS of Day 127 is acceptable as 5 half-lives will almost have passed between administration and final blood sampling.

Overall, the design of the Phase 1 study CT-P39 1.1 is in line with the "Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010). The study design is generally in agreement with the Scientific Advice (SA) received from the EMA in March 2019 (EMEA/H/SA/4063/1/2019/III) and October 2019 (EMEA/H/SA/4063/1/FU/1/2019/III).

As outlined in the October 2019 SA (EMEA/H/SA/4063/1/FU/1/2019/III), the third arm of this study, US-licensed Xolair, is not a requirement for an MAA in the EU. The inclusion of this arm is nevertheless acceptable, and the results can be considered supportive. As outlined in the October 2019 SA, Part 1 is not required for an EU MAA application and the objective of the sub study is unclear. In light of this, the assessment of biosimilar PK comparability focused on Part 2 of the study.

The study population included healthy subject (male or female) between the ages of 18 and 55 years inclusive, with a body weight of >40 kg and ≤90 kg and a BMI between 18.0 kg/m2 and 32.0 kg/m2 (both inclusive), and with a total IgE level of ≤100 IU/mL at screening. The eligibility range for BMI was outlined as between 18.0 and 29.9 kg/m2 (both inclusive), in the proposed protocol in the March 2019 SA (EMEA/H/SA/4063/1/2019/III). Additionally, the EMEA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) recommend an eligibility range of 18.5 and 30 kg/m2 for BMI. The lower and upper limits for BMI of 18.0 kg/m2 and 32.0 kg/m2 respectively for this study are outside the proposed range from the March 2019 SA and the EMEA Guideline on the Investigation of Bioequivalence. However, dose adjustment was not suggested for BMI as outlined in section 5.2 of the SmPC this range of BMI was deemed acceptable. The eligibility criteria are generally in line with the criteria discussed in the SA from October 2019 (EMEA/H/SA/4063/1/FU/1/2019/III). Overall, the inclusion and exclusion criteria for this study are acceptable.

A dose of 150 mg omalizumab was selected as a flat dose for each arm of the study. This is acceptable as it is within the dose range of 75 mg to 600 mg of omalizumab that shows linear PK characteristics. This dose is also within the approved dosing range for omalizumab. It is also in line with the dose

determination charts from Section 4.2 of the SmPC for Xolair for the inclusion criteria weight (>40 - 90 kg) and IgE (≤100 IU/mL) of the study.

Two batches of EU-approved Xolair were used in CT-P39 1.1. There was a minimal difference between the protein concentration of the two batches of EU-approved Xolair used in this study, so no impact of the different batches would have been expected. The majority of subjects (n=43) were administered one of the batches (batch AVXS234905) and the remaining subjects (n=6) received the new batch (batch AVXS241303). There was a notable difference in the primary PK parameters between the two batches, however as the number of subjects who received the second batch was small cautious interpretation of these differences is needed. The Applicant also provided a protein content adjusted PK analysis. Although not pre-specified, the results of this analysis are accepted as supportive of the primary analysis, and there was no notable difference between batches for the primary PK parameters when adjusted for protein content, with the 90% CIs lying between 0.8 – 1.25 and including unity.

The primary objective of Study CT-P39 1.1 was to demonstrate PK similarity of CT-P39 to both EU-approved Xolair and US-licensed Xolair, as well as to demonstrate similarity between EU-approved Xolair and US-licensed Xolair. As outlined in the August 2019 SA, for an EU MAA, the comparison between CT-P39 to EU-approved Xolair is of primary importance as EU-approved Xolair has also been used in the confirmatory efficacy study. The other comparisons can be considered supportive. Secondary objectives comprised of additional PK parameters to support similarity, comparison of safety and tolerability, and immunogenicity between CT-P39 and the reference products.

The primary endpoints were C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}last}$. This is in line with the relevant EMA guideline (EMA/CHMP/BMWP/403543/2010) for a single dose study with subcutaneous administration. $AUC_{0\text{-}last}$ is not a requirement under this guideline but there is no restriction to including this as an endpoint and it is accepted. The secondary PK endpoints comprised T_{max}, $T_{1/2}$, %AUCext, λz, CL/F, Vz/F.

In this PK study both treatments were administered subcutaneously. The subcutaneous route is acceptable to assess the absorption, distribution, and elimination phases of the treatment. Moreover, as both the test and reference products are for subcutaneous administration only this is acceptable without the need for additional PK parameters to waive the need for studies with intravenous administration as outlined in Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies –Non-clinical and Clinical Issues (EMA/CHMP/BMWP/403543/2010).

The duration of PK sampling time-points in this study are acceptable as they extend to cover 5 elimination half-lives of omalizumab. It is noted that daily time-points up to Day 10 could have been included to better characterise the C_{max} and T_{max} which is reached on average at 7-8 days (Xolair, SmPC).

The description regarding the planning of randomisation for Part 2 are considered reasonable. The randomisation was stratified by body weight, serum total IgE level, and sex (male versus female) and this is acceptable.

The statistical analysis methods for the primary analysis of part 2 of study CT-P39 1.1 are considered acceptable.

A total of 595 subjects were screened of which 419 subjects did not meet the eligibility criteria. Of the 176 subjects who met study criteria, 146 subjects participated in Part 2 of the study, and 30 subjects participated in Part 1 of the study.

In Part 2, total of 146 subjects were randomized to 1 of the 3 treatment groups: 46 to CT-P39, 47 to EU-approved Xolair, and 49 to US-licensed Xolair. A total of 142 (97.3%) subjects completed Part 2 of the study and the proportion of subjects who completed the study was similar in all 3 arms. 4 subjects (2.7%) discontinued the study after drug administration, with 2 due to withdrawal by subject, 1

subject lost-to follow-up, and 1 subject with the reason listed as other. The patient disposition is acceptable for Part 2.

There were three protocol amendments to the original protocol for this study. Any protocol amendments were implemented prior to the randomisation which is deemed acceptable.

There were no major protocol deviations reported during the study. Two subjects in Part 2 did not meet the inclusion or exclusion criteria. 1 subject in the CT-P39 group had taken a prohibited medication. The Applicant has provided sufficient justification that the medication used was not expected to have any major impact on the PK results. The second subject was also in the CT-P39 group and weighed over 90 kg at screening and at Day -1. The concomitant medication in this case is unlikely to have impacted then PK parameters of omalizumab in this study. For the subject who weighed >90 kg, weight was a covariate in this study and the subject's BMI was within the acceptable range, so it can be accepted that this one subjects body weight would have a minimal impact on PK outcomes.

In the ITT set for Part 2, the demographic and baseline characteristics were generally balanced. The majority of subjects were female (58.2%); the percentage of female subjects was slightly lower in the EU-approved Xolair group (55.1%) compared with the CT-P39 (59.6%) and US-licensed Xolair (60%) groups but were overall similar. The body weight was similar across the 3 groups which is important given the influence of body weight on exposure. Randomization was stratified by body weight, and the majority of subjects were <70 kg (54.8%) overall, and this was similar across the 3 arms of the study. Serum total IgE at screening was 34.2 IU/mL overall, and the majority of subjects fell <40 IU/mL IgE (64.4%). However, the percentage of subjects with ≥40 IU/mL IgE was higher in the CT-P39 arm (40.4%) than the EU-approved Xolair (32.7%) and the US-licensed Xolair (34%). Differences in total IgE levels at screening were not significant (p-value >0.05) between groups in the ANCOVA model and it was accepted that there would likely be no significant impact from the observed difference. The post-hoc analysis to compare the PK outcomes between the high and low IgE levels did not show consistency between groups, and it was accepted that the difference had no meaningful impact on the PK outcomes.

Small differences between groups with regards medical history and concurrent disease have been noted but overall, these differences are not considered important. There were a number of subjects in each of the CT-P39 (7, 14.9%), EU-approved Xolair (8, 16.3%) and US-licensed Xolair (8, 16.0%) reported to have a medical history of an immune system disorder. The summary of the PK parameters from the post-hoc analysis showed slightly lower AUC for subjects with a history of immune disorders in each group, however differences in C_{max} were inconsistent. Given the small number of subjects in each group with a medical history of immune disorders these results should be interpreted with caution. As this reduction was consistent between the CT-P39 and EU-approved Xolair groups, this difference does not impact the PK comparability assessment. Of the 146 subjects in the ITT set for Part 2, a total of 146 subjects (100%) received the IP and were included in the Safety and Pharmacokinetic sets. 2 subjects were excluded from the PD set; 1 subject each of CT-P39 and US-licensed Xolair groups, who showed BLQ values at all timepoints in both of total and free IgE results were excluded from the PD Set of Part 2. Therefore, a total of 144 (98.6%) subjects were included in the PD set. As no subjects were excluded from the PK set there are no issues with the numbers analysed.

Following a single SC dose of 150 mg omalizumab, the mean serum omalizumab concentration-time profiles for CT-P39, EU-approved Xolair and US-licensed Xolair were overall similar. However, omalizumab concentrations with CT-P39 were higher compared to EU-approved Xolair at the earlier time-points, approximately up to Day 15. The same trend was not strictly observed when looking at the individual PK concentration-time profiles; the concentration-time curves were generally similar,

with a number of subjects showing higher concentrations at the earlier time-points in the CT-P39 group compared to the EU-approved Xolair group.

The geometric mean for the C_{max} in the CT-P39 group (20.08 µg/mL) was higher than in the EU-approved Xolair group (18.24 µg/mL). A similar trend was seen for the geometric means for the $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$; both $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ were slightly higher in the CT-P39 group ($AUC_{0\text{-}last}$: 846.0 day·µg/mL; $AUC_{0\text{-}inf}$: 910.9 day·µg/mL) compared to the EU-approved Xolair ($AUC_{0\text{-}last}$: 843.8 day·µg/mL; $AUC_{0\text{-}inf}$: 897.7 day·µg/mL). In general, the C_{max} (19.43 µg/mL), $AUC_{0\text{-}last}$ (850.0 day·µg/mL), and $AUC_{0\text{-}inf}$ (926.3 day·µg/mL) for US-licensed Xolair group was also similar to the test and reference groups.

The median T_{max} was approximately 7 days in all 3 treatment groups. The CV% for t_{max} was moderate across groups (38.5% to 47.4%), with values ranging from 2 to 14 days for CT-P39 and 3 to 18 days for EU-approved Xolair. The geometric mean terminal half-life ($t_{1/2}$) in the CT-P39 group (28.16 days) was longer than in the EU-approved Xolair group (27.10 days).

The geometric mean terminal elimination rate constant (λz) appears similar in both the CT-P39 (0.02461 L/day) and the EU-approved Xolair group (0.02557 L/day). The geometric mean for apparent total body clearance (CL/F) is also similar in both the CT-P39 (0.1728 L/day) and the EU-approved Xolair groups (0.1751 L/day). The extrapolated part of the $AUC_{0\text{-}inf}$ i.e. the geometric mean for %AUCext, was generally small and similar for both the CT-P39 group (4.142%) and the EU-approved Xolair group (4.508%). An extrapolated AUC of ≤20% is considered to be acceptable (see *EMA Clinical pharmacology and pharmacokinetics: Q&A, 7. Biosimilars*). Overall, results for the secondary pharmacokinetic endpoints were similar between CT-P39 and EU-approved Xolair.

For the primary endpoints of $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$, for CT-P39 vs EU-approved Xolair, the geometric mean ratios (GMR), and the 90% CIs were within the 80-125% acceptance criteria. For $AUC_{0\text{-}last}$ the GMR was 104.00% with 90% CI of 94.96 – 113.89%, and for $AUC_{0\text{-}inf}$ the GMR was 105.62% with 90% CI of 95.91 – 116.31%. Both $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ included the 100% and are acceptable to show biosimilarity.

For the primary endpoint of C_{max}, for CT-P39 vs EU-approved Xolair, the GMRs and 90% CIs were within the 80-125% acceptance criteria. However, although the point estimate for GMR was 113.14%, the 90% CI ranged 103.15 – 124.11%. The upper bound of the CI was very close to the 125% limit for the acceptance criteria, and unity was not included in the 90% CI, suggesting that the C_{max} was substantially higher with the test CT-P39 than the reference EU-approved Xolair. The Applicant has provided a robust justification for the time-points selected and adequately cover the time-points from 5-9 days, including 7 days after administration, which lines up with the median T_{max} for CT-P39, EU-approved Xolair, and US-licensed Xolair. It is accepted that the sampling schedule in CT-P39 would have provided a reliable estimate of the C_{max} and T_{max}. The Applicant has also provided additional statistical analysis on the primary PK endpoints adjusted based on protein content of the batch used for each subject. The C_{max} and 90% CIs of ratios of geometric mean were within 0.8 – 1.25 when adjusted for protein content, and each comparison included unity. Although this analysis was not pre-specified and would not be acceptable to prove a failed PK comparability result, this analysis is acceptable as supportive of the primary analysis in the conclusion of PK comparability. As the C_{max}/T_{max} were adequately covered by the sampling schedule, the 90% CI for the C_{max} was contained with the 0.8 – 1.25 range, and the protein content corrected analysis is supportive of the primary analysis, it can be concluded that PK comparability has been demonstrated for CT-P39 with EU-approved Xolair.

The Applicant has provided no subgroup analyses for this Study CT-P39 1.1. In general, this is acceptable as no subgroup analyses were prespecified. Additionally, in line with EMEA Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010), subgroup analyses are only expected if patients from different

global regions are included; the demographics of the study population for Part 2 were predominantly white (78.1%), and the PK of omalizumab do not suggest any adjustments are needed based on ethnicity.

The incidence of post-treatment ADA was lower in CT-P39 group (1, 2.1%) than the EU-approved Xolair group (13, 26.5%). NAb was not detected in the CT-P39 group and was detected in 1 subject in the EU-approved Xolair group. There was no subject with an increasing trend in ADA titre after treatment, and the majority had low ADA titre. Although there was a generally low incidence of ADA and NAb in this study, there was a difference between the incidence in CT-P39 and EU-approved Xolair. The Applicants position that there was no apparent impact of ADAs on PK results as presented is accepted. These results should be interpreted cautiously due to the overall low incidence of ADA in this study.

As previously mentioned, Part 1 of Study CT-P39 1.1 was not required for the MAA in the EU. The Applicant has presented the results of Part 1 as part of the CSR CT-P39 1.1 but has presented them separately as part of the report. This is acceptable and in line with the SA received.

Following a single SC administration of CT-P39 or EU-approved Xolair, the mean serum concentrations of omalizumab at each timepoint up to Day 127 were generally comparable to Part 2 and showed a similar trend in the decreasing omalizumab concentration over time as Part 2 also. The values for the PK parameters in Part 1 were overall similar to the values for the primary PK parameters in Part 2. Part 1 showed the same trend seen in Part 2 where the means and for C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were higher in the CT-P39 group than the EU-approved Xolair group. For example, the mean C_{max} in for CT-P39 Part 1 (20.29 µg/mL) and Part 2 (20.08 µg/mL) were higher than the mean for EU-approved Xolair in Part 1 (17.69 µg/mL) and Part 2 (18.24 µg/mL) respectively. The other secondary PK parameters investigated in both Part 1 and Part 2 were overall similar.

The sample size of 30 subjects randomized in 1:1 ratio to receive a single dose (150mg) of CT-P39 or EU-approved Xolair was not powered to draw any meaningful conclusions regarding the PK comparability of CT-P39 to EU-approved Xolair, and as such the assessment of Part 1 is supportive of the results seen in Part 2.

Secondary Pharmacokinetics of Study CT-P39 3.1

CT-P39 3.1 was a double-blind, randomized, active-controlled, parallel group, multi-centre, Phase 3 study to evaluate the efficacy and safety of CT-P39 compared with EU-approved Xolair, when SC administered as an add-on therapy for the treatment of patients with CSU who remain symptomatic despite an approved dose of nonsedating H1-antihistamine treatment. One of the secondary objectives in patients with CSU was comparison C_{trough} levels of omalizumab between CT-P39 and EU-approved Xolair. A full assessment of the study design for CT-P39 3.1 is detailed in Section 2.6.6 Discussion on clinical efficacy.

The study design for Part I and Part II of this study is acceptable for assessing the C_{trough} of omalizumab between CT-P39 and EU-approved Xolair. The re-randomization of Arm 2 after Period I into a switching (to 300 mg CT-P39) or non-switching (remain on EU-approved Xolair) is acceptable to assess if there is any effect on drug concentration if switching from EU-approved Xolair to CT-P39.

A secondary objective of CT-P39 3.1 was to assess pharmacokinetics of CT-P39 compared to EU-approved Xolair. For this purpose, the C_{trough} levels were measured pre-dose at Week 0, 4, 8, 12 in Treatment Period I and Weeks 16, 20, and 24 in Treatment Period 2. For PK assessment in CSU patients, no equivalence range has been pre-defined, and results are summarized descriptively.

For Treatment Period I the mean omalizumab C_{trough} levels were similar between Arm 1 (CT-P39 300 mg) and Arm 2 (EU-approved Xolair 300 mg) and were similar between Arm 3 (CT-P39 150 mg) and

Arm 4 (EU-approved Xolair 150 mg) at all time-points. The mean C_{trough} of 300 mg CT-P39 and 300 mg EU-approved Xolair groups were higher, approximately double, compared to the mean serum concentrations of 150 mg CT-P39 and 150 mg EU-approved Xolair groups. This is in line with what would be expected given the larger dose.

Arm 2-1, which assessed the switch from EU-approved Xolair to CT-P39, saw a larger increase in C_{trough} between Week 12 (31.5079 µg/mL) and Week 16 (35.3776 µg/mL) than both Arm 1 and Arm 2-2. This increase was maintained up to Week 24 indicating steady state had been achieved. Arm 2-2 did not see the same large increase between Week 12 (31.3568 µg/mL) and Week 16 (32.6859 µg/mL) and in general, was slightly lower at all time-points in Treatment Period II than either Arm 1 or Arm 2-1. In Arm 1, Arm 2-1, and Arm 2-2 there was a general trend of an increase in mean C_{trough} between Week 12 and 16, however this increase was notably larger in Arm 2-1 which is the treatment arm designed to show if there is any effect when switching from EU-approved Xolair to CT-P39. The Applicant has provided sufficient discussion on the difference seen in trough omalizumab levels between Arm 2-1 and Arm 2-2 at Week 16. It is accepted that subjects in Arm 2-1 showed slightly higher trough concentrations than Arm 2-2 in Treatment Period 1, and so the difference seen in trough levels at Week 16 in Treatment Period 2 was due to interpatient variation between Arm 2-1 and Arm 2-2.

For treatment Arm 3 and Arm 4 the C_{trough} increased substantially between Week 12 and 16 and showed an almost 2-fold increase by Week 24, which is expected given the increase in dose to 300mg for both treatment arms. The mean C_{trough} in Arm 3 and Arm 4 groups showed comparable increases over time; however, the C_{trough} in Arm 4 was slightly higher than Arm 3 at all time-points in both treatment periods.

A subgroup analysis was conducted to evaluate the impact of age on PK of omalizumab, at Week 12. Adolescent (age 12-17), adult (age 18-64) and elderly (age 65 and up) patients were compared for all treatment groups. In general, C_{trough} values were in line with the results at Week 12 for the combined analysis for the 18 to 64 age group for all treatment arms. The C_{trough} values were higher in the 12 to 17 years age groups in all treatment arms and C_{trough} values were lower in the ≥65 years age group in all treatment arms. The numbers of patients included in the adolescent and the elderly subgroups of each treatment group are too small to draw any meaningful conclusions from this analysis.

Overall, the C_{trough} values were comparable between CT-P39 and the corresponding EU-approved Xolair groups for all timepoints during Treatment Period I and Treatment Period II.

Discussion on Pharmacodynamics

Pharmacodynamics of CT-P39 1.1

The assessment of pharmacodynamics was a secondary objective of CT-P39 1.1. The Applicant has investigated the effect of a single dose CT-P39, EU-approved Xolair, US-licensed Xolair on the concentrations of Free IgE and Total IgE in healthy subjects. These are acceptable PD parameters given the mechanism of action of omalizumab is to bind to free IgE to inhibit IgE mediated inflammation.

The mean Free IgE serum concentrations show a similar trend similar at the measured timepoints between the CT-P39, EU-approved Xolair, and US-licensed Xolair groups; free IgE is rapidly suppressed to a similar concentration in all 3 groups, and gradually recovers over time. For the secondary PD endpoints of free IgE, the Cmin of free IgE was similar between CT-P39 (3.5267 IU/mL) and EU-approved Xolair (3.559 IU/mL). The median Tmin of free IgE was lower for CT-P39 (3.000 days) compared with EU-approved Xolair (5.051 days). The mean maximum % decrease of free IgE from baseline was higher in CT-P39 (73.05%) compared with EU-approved Xolair (64.20%). Total IgE was a stratification factor for this study and following stratification the percentage of subjects with ≥40 IU/mL IgE at baseline was higher in the CT-P39 arm (40.4%) than the EU-approved Xolair (32.7%)

and the US-licensed Xolair (34%). The Applicant has provided sufficient discussion on the impact of the baseline IgE on the analysis of the pharmacodynamic outcomes of this study. The slight difference in the baseline IgE between the CT-P39, and EU-approved Xolair and US-licensed Xolair, impacted the % reduction in free IgE between groups. Although there were differences in the % reduction of free IgE, it is accepted that CT-P39 was able to deplete free IgE levels to the same degree as originator omalizumab. The free IgE outcomes for US-licensed Xolair group are similar to CT-P39 and US-licensed Xolair groups.

The mean total IgE serum concentration shows a broadly similar trend between the 3 treatment groups CT-P39, EU-approved Xolair, and US-licensed Xolair; total IgE increases following drug administration, and gradually recovers to baseline over time. For the secondary PD endpoints, the T_{max} of total IgE was very similar between CT-P39 (28.191 days) and EU-approved Xolair (28.156 days). The mean (SD) C_{max} of total IgE was higher in the CT-P39 group (245.2391 IU/mL, SD 223.24856) compared with the EU-approved Xolair group (174.2857 IU/mL, SD 145.17432). There was a high level of variability for the C_{max} of total IgE, with the CV% for CT-P39 group being 91% and for EU-approved Xolair being 83%. The mean maximum % increase of total IgE saw a similar outcome, with a higher mean % increase for CT-P39 (574.26%, SD 309.426) in comparison to EU-approved Xolair (494.45%, SD 235.443). The Applicant explains this is caused by inter-subject variability and aberrant values and this is acknowledged by the CHMP.

Pharmacodynamics of CT-P39 3.1

The assessment of total and free serum IgE was a secondary objective of CT-P39 3.1. The Applicant investigated the effect of treatment with CT-P39 and EU-approved Xolair on the concentrations of Free IgE and Total IgE in CSU patients. These are acceptable PD parameters given the mechanism of action of omalizumab is to bind to free IgE to inhibit IgE mediated inflammation.

For Treatment Period I, the mean baseline IgE was lower in the CT-P39 arms (Arm 1, 210.01 IU/mL; Arm 3, 144.67 IU/mL) than in the EU-approved Xolair groups (Arm 2, 260.62 IU/mL; Arm 4, 262.08 IU/mL). Total IgE was shown to increase 2-3 fold from baseline at Week 4, following administration of omalizumab in all 4 treatment arms. The total IgE remained increased in all treatment arms up to Week 12. There were differences in the total Serum IgE at Week 12 (Arm 1, 646.90 IU/mL; Arm 2, 782.61 IU/mL; Arm 3, 495.43 IU/mL; Arm 4, 627.71 IU/mL), however taking into account the differences in baseline total IgE, these differences at Week 12 are generally proportional to the baseline IgE. The mean baseline free IgE was lower in the CT-P39 Arm 1 (61.1246 IU/mL) compared with the EU-approved Xolair Arm 2 (70.0912 IU/mL). Free IgE was shown to be supressed compared to baseline in all arms at Week 4 and remained suppressed up to Week 12. Free IgE was suppressed to lower levels in the 300 mg arms (Arm 1, 3.8382 IU/mL; Arm 2, 3.1425 IU/mL) than in the 150 mg arms (Arm 3, 5.6388 IU/mL; Arm 4, 4.5283 IU/mL) at Week 12.

For Treatment Period II, mean total IgE remained increased in all treatment groups however there was a notable difference in mean IgE between Arms 2-1 (846.25 IU/mL) and Arm 2-2 (717.96 IU/mL) at Week 16, showing a difference after transition from EU-approved Xolair to CT-P39. It is understood and accepted that the difference in total IgE levels between Arm 2-1 and Arm 2-2 is generally proportional to the baseline IgE levels for each group. Overall, the difference in mean total IgE at seen at Week 12 was proportional to the baseline mean total IgE, and the curves from Arm 2-1 and Arm 2-2 showed similar shapes From Week 12 until termination. The mean baseline free IgE remained suppressed to similarly low levels in Arm 1, Arm 2-1, and Arm 2-2. There was no notable change between the mean free IgE concentrations between Arm 2-1 and Arm 2-2. This indicates that the patients that transitioned from EU-approved Xolair to CT-P39 were not different than patients maintained on either EU-approved Xolair or CT-P39 with regards to free IgE. Mean free IgE was further suppressed in Arm 3 and Arm 4 at Week 16, following the transition to a 300 mg dose of omalizumab.

Overall, the mean total and free serum IgE was generally comparable between the CT-P39 arms and the EU-approved Xolair arms. All groups showed an increase in mean total IgE and a suppression of free IgE. There was an increase in mean total IgE when transitioning from EU-approved Xolair to CT-P39, however mean free IgE was not affected, indicating there was no difference between the groups.

Product information

The information on clinical pharmacology in the proposed SmPC is in line with that of the reference product.

2.6.4. Conclusions on clinical pharmacology

PK comparability has been demonstrated according to the pre-specified acceptance criteria; the GMRs and 90% CIs were within the 80-125% acceptance criteria for the primary PK endpoints of $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}. The GMRs and 90% CIs for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} are acceptable.

In study CT-P39 1.1 pharmacodynamics of CT-P39 and EU-approved Xolair were assessed by measuring free IgE and total IgE as secondary outcomes to the study in healthy subjects. CT-P39 1.1 showed that the pharmacodynamic parameters for free IgE and total IgE in healthy subjects were overall similar. In Study CT-P39 3.1 the total IgE and free IgE were measured in patients with CSU as a safety endpoint. CT-P39 3.1 showed that the mean total IgE was increased and mean free IgE was suppressed in both the CT-P39 arms and the EU-approved Xolair arms similarly.

Overall, the pharmacokinetics and pharmacodynamics of CT-P39 were similar to EU-approved Xolair, and the applicants conclusions on the comparability of pharmacokinetics and pharmacodynamics of CT-P39 and EU-approved Xolair is accepted.

2.6.5. Clinical efficacy

In order to demonstrate similarity in efficacy between CT-P39 and Xolair, a randomised, active-controlled, parallel group, phase 3 study was conducted in adult patients with Chronic Spontaneous Urticaria Who Remain Symptomatic despite H1-antihistamine Treatment.

Study CT-P39 3.1 was not aimed to demonstrate efficacy per se, but to demonstrate the equivalent efficacy of CT-P39 and Xolair, and to confirm that there were no clinically meaningful differences between CT-P39 and Xolair in terms of safety and immunogenicity to support overall clinical biosimilarity of CT-P39 and Xolair.

Table 15: Overview of Clinical Efficacy Study Program for CT-P39 in Patients with CSU

Study ID	Design	Study Posology	No. of Subjects Randomized	Study Duration	Study Population	Efficacy Endpoint
CT-P39 3.1	Phase 3 double-blind, randomized, active-controlled, parallel-group study to compare efficacy and safety of CT-P39 and Xolair	**Treatment Period I** • 300 mg or 150 mg of CT-P39 and Xolair were subcutaneously administered using PFS on Weeks 0, 4, and 8 **Treatment Period II** • 300 mg of CT-P39 and Xolair were subcutaneously administered using PFS on Weeks 12, 16, and 20	<Actual> **Treatment Period I** **Total= 619** • Arm 1:204 • Arm 2:205 • Arm 3:107 • Arm 4:103	The maximum duration of the study per patient will be 44 weeks • Screening: -W4~W0 • TP I: W0~W12 • TP II: W12~W24 • Follow up: W24~W40	Patients with CSU who remain symptomatic despite H1-antihistamine treatment	**Primary Efficacy Endpoint:** • Change from baseline in ISS7 of 300 mg of CT-P39 (Arm 1) and 300 mg of Xolair (Arm 2) at Week 12 **Secondary Efficacy Endpoints:** • Change from baseline in ISS7 at Weeks 8 and 24 • Time to minimally important difference (MID; reduction of ≥ 5 points from baseline) response in ISS7 by Week 12 • Percentage of MID responders in ISS7 at Weeks 8, 12, and 24 • Relative potency of CT-P39 compared with Xolair as determined by change from baseline in ISS7 at Week 12 • Change from baseline in UAS7 at Weeks 8, 12, and 24 • Percentage of patients with UAS7 of ≤ 6 points at Weeks 8, 12, and 24 • Percentage of complete responders (UAS7 = 0) in UAS7 at Weeks 8, 12, and 24 • Change from baseline in the weekly hives severity score at Weeks 8, 12, and 24 • Percentage of angioedema-free days from Weeks 4 to 12 • Change from baseline in number of tablets/week of rescue therapy at Week 8, 12, and 24 **Secondary Quality of Life Endpoints:** • Change from baseline in the overall DLQI score at Weeks 12 and 24 • Change from baseline in the overall CU-Q$_2$oL at Weeks 12 and 24

2.6.5.1. Dose response studies

No dose response studies were performed and are not deemed necessary in the biosimilarity setting.

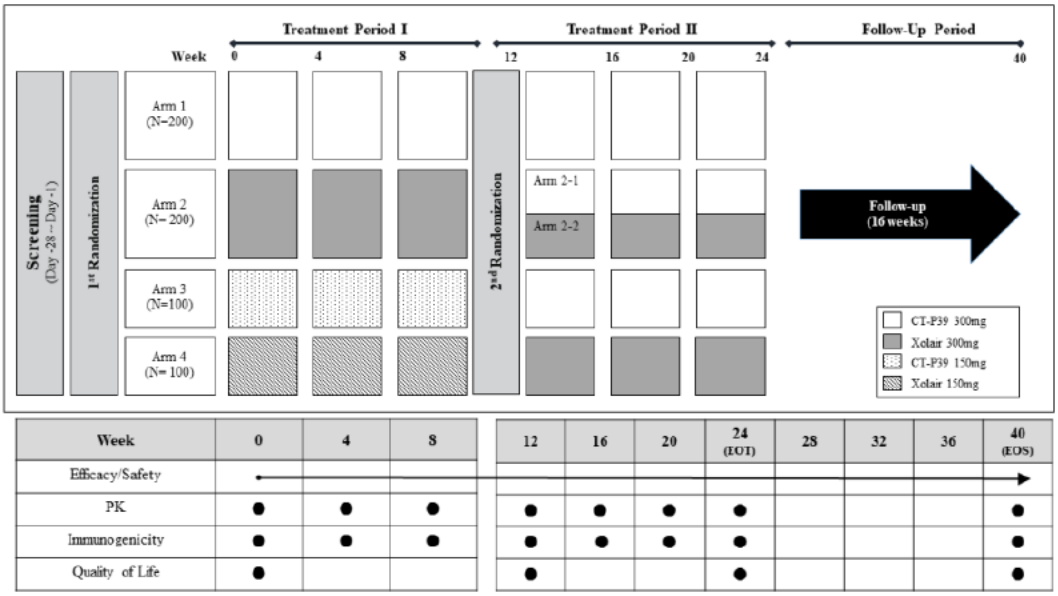
2.6.5.2. Main study

A Double-blind, Randomised, Active-controlled, Parallel Group, Phase 3 Study to Compare Efficacy and Safety of CT-P39 and Xolair in Patients with Chronic Spontaneous Urticaria Who Remain Symptomatic despite H1-antihistamine Treatment (CT-P39 3.1)

Methods

This was a double-blind, randomised, active-controlled, parallel group, multi-centre, Phase 3 study to evaluate the efficacy and safety of CT-P39 compared with Xolair, when SC administered as an add-on therapy for the treatment of patients with CSU who remain symptomatic despite an approved dose of nonsedating H1-antihistamine treatment.

Approximately 600 male and female patients with CSU, aged between 12 and 75 years (both inclusive), were planned to be enrolled and randomised to 300 mg of CT-P39, 300 mg of Xolair, 150 mg of CT-P39, and 150 mg of Xolair in a 2:2:1:1 ratio in Treatment Period I. All patients who completed Treatment Period I underwent the second randomisation process prior to the study drug administration at Week 12 and entered Treatment Period II. Patients who were initially randomised to 300 mg of Xolair (Arm 2) in Treatment Period I were re-randomised in a ratio of 1:1 to switching arm (Arm 2-1) or non-switching arm (Arm 2-2) (Figure 5). All patients continued to concomitantly receive an approved dose of nonsedating H1-antihistamine treatment throughout the study. The overall study duration was 44 weeks including Screening Period (4 weeks), Treatment Period I (12 weeks), Treatment Period II (12 weeks), and Follow-up Period (16 weeks).



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

Abbreviations: EOS = End-of-study; EOT = End-of-treatment; N = Total number of patients; PK = Pharmacokinetics.

Figure 5. Study Design Overview

Screening Period (4 Weeks)

Screening evaluations were completed within 28 days prior to the first study drug administration on Day 1 (Week 0). Patients' eligibility and baseline symptom scores were assessed. Patients started to receive an approved dose of protocol-defined nonsedating H1-antihistamine from at least 3 consecutive days prior to start of patient electronic diary (eDiary) record for baseline ISS7 (Day -7 to Day -1) in the Screening Period and continued taking the same dose throughout the study. Patients were instructed to complete the patient eDiary twice daily (morning and evening) from screening and throughout the study.

Treatment Period I (12 Weeks)

On Day 1 (Week 0), approximately 600 patients who met all of the inclusion criteria and none of the exclusion criteria were to be randomly assigned in a 2:2:1:1 ratio to one of the 4 treatment arms:
- Arm 1 (200 patients): 300 mg of CT-P39
- Arm 2 (200 patients): 300 mg of Xolair
- Arm 3 (100 patients): 150 mg of CT-P39
- Arm 4 (100 patients): 150 mg of Xolair

The patients received 3 doses of CT-P39 or Xolair as SC injections using a pre-filled syringe (PFS) Q4W for 12 weeks. The randomisation was balanced by using permuted blocks and was stratified by baseline ISS7 (< 13 points versus ≥ 13 points), body weight (BW) on Day 1 (< 80 kg versus ≥ 80 kg), and country. For patients who received one (150 mg) injection of study drug, an additional 1 mL placebo injection using a PFS was administered to maintain the study blind between the 2-dose levels (300 mg versus 150 mg). Efficacy, PK, QoL, safety, and immunogenicity data were collected, and the primary endpoint was measured prior to the study drug administration at Week 12.

Treatment Period II (12 Weeks)
All patients who completed Treatment Period I underwent the second randomisation process prior to the study drug administration at Week 12 and entered Treatment Period II to receive additional 3 doses of study drug Q4W.

Patients were stratified by decrease from baseline in ISS7 at Week 12 (≥ 5 points versus < 5 points) and BW at Week 12 (< 80 kg versus ≥ 80 kg). During Treatment Period II, patients who were initially randomized to 300 mg of Xolair (Arm 2) in Treatment Period I were re-randomized in a ratio of 1:1 to switching arm (Arm 2-1) or non-switching arm (Arm 2-2).

Patients assigned to switching arm (Arm 2-1) underwent transition to 300 mg of CT-P39 and patients assigned to non-switching arm (Arm 2-2) continued 300 mg of Xolair. All patients who were initially randomly assigned to Arm 1 (300 mg of CT-P39) during Treatment Period I continued to receive the same drug. All patients who were initially randomly assigned to Arm 3 (150 mg of CT-P39) or Arm 4 (150 mg of Xolair) during Treatment Period I continued to receive the same drug at an increased dose of 300 mg until end-of-treatment (EOT) visit.

All patients received 3 doses of either 300 mg of CT-P39 or 300 mg of Xolair Q4W for 12 weeks during Treatment Period II. The last dose of study drug during Treatment Period II was given at Week 20 study visit and the EOT visit was performed at Week 24.

Patients who discontinued the study drug during any of the treatment periods also returned to the study centre by regular scheduled time intervals and conducted all planned clinical assessments including efficacy, QoL, safety, and immunogenicity, except for the PK assessment for which the sample were collected only at the right next scheduled visit of the last study drug administration visit and EOS visit.

Follow-up Period (16 Weeks)

All patients will enter the Follow-up Period and be followed up for 16 weeks to assess additional efficacy, PK, QoL, safety, and immunogenicity data. Visits will be scheduled Q4W, and the end-of-study (EOS) visit will occur at Week 40. At the EOS visit, additional assessments including efficacy, PK, QoL, safety, and immunogenicity assessments will be performed.

During the Follow-up Period, no study drug will be given and increasing the dose of the current nonsedating H1-antihistamine treatment is not permitted. Patients may add one additional nonsedating H1-antihistamine, if required. Patients who discontinue the study drug during the treatment periods may start adding one additional nonsedating H1-antihistamine from the next regular visit of the last study drug administration visit. The goal of allowing additional H1-antihistamine therapy during the follow-up period is to reduce patient dropout for further evaluation.

- **Study Participants**

Main inclusion criteria:

- Male or female between 12 and 75 years of age (both inclusive; age limits was dependent on country-specific regulation).
- Had been diagnosed with CSU for at least 6 months prior to the first study drug administration.
- Must have been diagnosed as CSU refractory to H1-antihistamine defined as below:
    - Presence of hives associated with itching for ≥ 6 consecutive weeks at any time prior to the first study drug administration despite current use of H1-antihistamine treatment for this time period.
    - Weekly itch severity score (range 0 to 21 points) ≥ 8 points and UAS7 (range 0 to 42 points) ≥ 16 points in 7 consecutive days (Day -7 to Day -1) prior to the first study drug administration.
    - Documented use of an approved dosage of nonsedating H1-antihistamine for CSU for at least 3 consecutive days immediately prior to start of patient eDiary record for baseline ISS7 (Day -7 to Day -1).

Main exclusion criteria

- Had a chronic urticaria with clearly defined underlying etiology (eg, physical urticaria such as acute, solar, cholinergic, heat, cold, aquagenic, pressure or contact) other than CSU or any disease with symptoms of urticaria or angioedema (eg, urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary or acquired angioedema, lymphoma, leukemia, or generalized cancer).
- Had a BW of < 30 kg.
- Had a medical history of and/or current disease including any of the following:
    - History of clinically significant allergic reaction and/or hypersensitivity to any component of omalizumab, Chinese hamster ovary cell products, other recombinant human or humanized antibodies, H1-antihistamines, or dry natural rubber (a derivative of latex).
    - History of and/or concomitant myocardial infarction.
    - History of anaphylactic shock.
    - History of and/or concomitant immune complex disease (including allergic reaction Type III), hyperimmunoglobulin E syndrome, autoimmune disease, or bronchopulmonary aspergillosis.
    - Any active skin disease associated with itch including atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, or senile pruritus.
    - A known infection with human immunodeficiency virus (HIV), hepatitis B, hepatitis C, or any active infection requiring treatment, except adequately treated and completely recovered past infections.
    - Any active malignancy or history of malignancy except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ.
- Had a history of and/or a current use of medications including any of the following:
    - Treatment with omalizumab or other monoclonal antibodies, protein, fusion protein, or other biologic agent targeting IgE.
    - Treatment with an investigational drug within 4 weeks or 5 half-lives (whichever was longer) prior to the first study drug administration.
    - Routine administration (ie, daily or every other day for ≥ 5 consecutive days) of systemic glucocorticoids, hydroxychloroquine, methotrexate, cyclosporine, azathioprine, cyclophosphamide, tacrolimus, or mycophenolate mofetil within 5 weeks prior to the first study drug administration.
    - Intravenous immunoglobulin G (IgG) or plasmapheresis within 5 weeks prior to the first study drug administration.
    - Regular (ie, daily or every other day for ≥ 5 consecutive days) use of oral doxepin within 3 weeks prior to the first study drug administration.
    - Use of any H2-antihistamine or LTRA within 2 weeks prior to the first study drug administration (However, continuing H2-antihistamine or LTRA treatment for disease other than CSU was allowed).
    - Use of beta-blocker therapy within 2 weeks prior to the first study drug administration.
    - Use of H1-antihistamines at greater than approved doses from 3 days prior to the start of patient eDiary record for baseline ISS7 (Day -7 to Day -1).

- Diagnosed with parasitic diseases or colonization on stool evaluation for ova and parasites (stool ova and parasite examination should be performed in patients who meet both the following criteria):
    - Correspond to any of risk factors for parasitic disease:
        - Travelled within 6 months prior to the first study drug administration or living in an endemic area of parasitic infections.
        - Chronic gastrointestinal symptoms.
        - Chronic immunosuppression.
    - Absolute eosinophil count > 2 × upper limit of normal (ULN).

- **Treatments**

During Treatment Period I, the patients received **300 mg or 150 mg of CT-P39 or Xolair SC** using a PFS Q4W for 12 weeks (total 3 doses, 1 each given on Weeks 0, 4, and 8) as per the first randomization.
Patients remained in study center for 2 hours after study drug administration for anaphylaxis observation.

During Treatment Period II, patients received 300 mg of CT-P39 or Xolair SC using a PFS Q4W for 12 weeks (total 3 doses, 1 each given on Weeks 12, 16, and 20) as per the second randomization. Patients remained in study center for an hour after study drug administration for anaphylaxis observation.

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

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

The study drug was administered SC to patients in the deltoid region of the right or left arm. Alternatively, the injections were administered in the thigh if medically significant reasons precluded administration in the deltoid region. The second injection was administered at an injection site other than the first injection site, at least 2.5 cm (or 1 inch) from the area used previously.

Table 16: Study Products, Dose and Mode of Administration, Batch Numbers

Product	Dose and Mode of Administration	Supplied as	Batch/Lot Numbers (Expiry Date)
CT-P39 (Test product)	150 mg or 300 mg by SC injection	PFS containing 150 mg/mL (150 mg/1 mL) of CT-P39	CTP39CLN2 (Mar-2021) CTP39CLN4 (Dec-2021) CTP39CLN5 (May-2023)
EU-approved Xolair (Reference product)	150 mg or 300 mg by SC injection	PFS containing 150 mg/mL (150 mg/1 mL) of omalizumab	AVXS241303 (Mar-2021) AVXS245405 (Jul-2021) AVXS246605 (Nov-2021) AVXS247507 (Nov-2021) AVXS248005 (Nov-2021) AVXS248603 (Dec-2021) AVXS250004 (Feb-2022) AVXS250006 (Feb-2022) AVXS250201 (Feb-2022) AVXS250213 (Feb-2022) AVXS251605 (Apr-2022) AVXS254902 (Aug-2022) AVXS259107 (Apr-2023) AVXS260005 (Apr-2023) AVXS260007 (Apr-2023) AVXS262002 (Aug-2023)

Abbreviations: EU = European Union; PFS = Pre-filled syringe; SC = Subcutaneous.

In this study, EU-approved Xolair was used as reference drug.

Identity of Placebo Product

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

The placebo contained the same ingredients as the Xolair formulation listed above, excluding omalizumab.

Concomitant medications

All patients were allowed to take one of the pre-defined nonsedating H1-antihistamines at approved dose throughout the study. The nonsedating H1-antihistamines and doses allowed during the study were as follows (the drug and dose in the following list were used in line with local approval status):

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

Patients started taking approved dose of H1-antihistamine for CSU from at least 3 consecutive days prior to the start of patient eDiary record for baseline ISS7 (Day -7 to Day -1) in the Screening Period and maintained the stable nonsedating H1-antihistamine treatment regimen throughout the study.

Increasing the dose of the nonsedating H1-antihistamine treatment was not permitted throughout the study.

Rescue Therapy
Predefined nonsedating H1-antihistamines at approved dose, in addition to being used as background medication, was allowed as rescue therapy for itch relief on an as-needed basis throughout the study. The selection of the rescue medication was to be made once for an individual patient. A switch of the rescue medication for an individual patient was not permitted.

Epinephrine
During the study, patients were supplied with epinephrine auto-injector (or local standard of care, in case of epinephrine auto-injector was not available) for treatment of anaphylactic reactions at the Investigator's discretion.

Prohibited medications
As outlined in the exclusion criteria section the routine administration (ie, daily or every other day for ≥ 5 consecutive days) of systemic glucocorticoids, hydroxychloroquine, methotrexate, cyclosporine, azathioprine, cyclophosphamide, tacrolimus, or mycophenolate mofetil within 5 weeks prior to the first study drug administration were prohibited.

Other prohibited medication included:

- Regular (ie, daily or every other day for ≥ 5 consecutive days) use of oral doxepin within 3 weeks prior to the first study drug administration.
- Use of any H2-antihistamine or LTRA within 2 weeks prior to the first study drug administration (However, continuing H2-antihistamine or LTRA treatment for disease other than CSU was allowed).
- Use of beta-blocker therapy within 2 weeks prior to the first study drug administration.
- Use of H1-antihistamines at greater than approved doses from 3 days prior to the start of patient eDiary record for baseline ISS7 (Day -7 to Day -1).

- **Objectives**

The **primary objective** of the study was:

- To demonstrate the equivalence of CT-P39 to Xolair at a dose of 300 mg in terms of efficacy in patients with CSU as determined by change from baseline in ISS7 at Week 12.

The **secondary objectives** of the study were:

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

- **Outcomes/endpoints**

The **primary efficacy endpoint** was the change from baseline in ISS7 of 300 mg of CT-P39 (Arm 1) and 300 mg of Xolair (Arm 2) at Week 12.

The **secondary efficacy endpoints** were:

- Relative potency of CT-P39 compared with Xolair as determined by change from baseline in ISS7 at Week 12.
- Change from baseline in ISS7 at Weeks 8 and 24.

- Time to minimally important difference (MID; reduction of ≥ 5 points from baseline) response in ISS7 by Week 12.
- Percentage of MID responders in ISS7 at Weeks 8, 12, and 24.
- Change from baseline in weekly urticaria activity score (UAS7) at Weeks 8, 12, and 24.
- Percentage of patients with UAS7 of ≤ 6 points at Weeks 8, 12, and 24.
- Percentage of complete responders (UAS7 = 0) in UAS7 at Weeks 8, 12, and 24.
- Change from baseline in the weekly hives severity scores (HSS7) at Weeks 8, 12, and 24.
- Percentage of angioedema-free days from Weeks 4 to 12.
- Change from baseline in number of tablets/week of rescue therapy at Weeks 8, 12, and 24.

Efficacy Assessments

Data for efficacy assessments were collected via patient eDiary. Patients were instructed to complete the patient eDiary twice daily (morning and evening) from Screening until EOS visit. The data collected for 7 consecutive days (Day -7 to Day -1) prior to the Day 1 visit was used as the baseline data for weekly score. The patient eDiary questions for efficacy assessments consisted of UAS7; ISS7 and HSS7, angioedema episodes, and rescue medication use.

Itch Severity Score
The itch severity score (ISS) was recorded twice daily (morning and evening) in the patient eDiary on a scale of 0 (none) to 3 (severe) points. The daily ISS is the average of morning and evening scores and the ISS7 is the sum of the daily ISS over 7 days. The MID is the smallest difference in scores considered clinically meaningful. The MID for ISS7 is defined as a reduction of 5 points or more from baseline.

Hives Severity Score
The HSS, defined by number of hives, was counted twice daily (morning and evening) in the patient eDiary, on a scale of 0 (none) to 3 (intense) points. The daily HSS is the average of the morning and evening scores, and the HSS7 is the sum of the daily HSS over 7 days.

Urticaria Activity Score
The UAS was calculated as the sum of the ISS and the HSS by diary-based documentation.
The sum of the scores represented disease severity on a scale from 0 (minimum) to 6 (maximum). The daily UAS is the average of the morning and evening scores and the UAS7 is the sum of the daily UAS over 7 days.

Angioedema Episodes
A patient recorded information regarding angioedema episodes daily in the patient eDiary. It was checked whether there was a rapid swelling on face, inside mouth, or elsewhere on the body and the actions and/or treatments were taken related to those angioedema occurrences.

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

Quality of Life Assessments
The patient recorded the validated DLQI and CU-Q2oL scores in the eDiary at the scheduled time points specified in the SOEs.

- **Sample size**

A total of 600 patients will be randomized in a 2:2:1:1 ratio to 300 mg of CT-P39 (Arm 1), 300 mg of Xolair (Arm 2), 150 mg of CT-P39 (Arm 3) and 150 mg of Xolair (Arm 4) treatment arms, respectively.

For the demonstration of the therapeutic similarity between 300 mg of CT-P39 (Arm 1) and 300 mg of Xolair (Arm 2) in the mean change from baseline in ISS7 at Week 12, a sample size of 400 patients (200 patients per each arm) achieved approximately 83% statistical power based on the two one-sided 2.5% significance level and an equivalence margin of [- 2.0, + 2.0]. In the sample size calculation, the common SD of the mean change from baseline in ISS7 at Week 12 was assumed to be 5.95 and the expected mean difference to be 0.

In order to support assay sensitivity and to evaluate the relative potency between CT-P39 and Xolair, additional 200 patients will be enrolled in 150 mg dose arms (100 patients in each of CT-P39 [Arm 3] and Xolair [Arm 4] treatment arms).

- **Randomisation and blinding (masking)**

An interactive web response system (IWRS) was used for randomization. Unblinded biostatisticians generated the randomization schedule for IWRS, which linked sequential patient randomization numbers to treatment arms. Patients were randomly assigned on Day 1 (Week 0) to receive 300 mg of CT-P39 (Arm 1), 300 mg of Xolair (Arm 2), 150 mg of CT-P39 (Arm 3) or 150 mg of Xolair (Arm 4) using a 2:2:1:1 allocation ratio. The randomization to treatment assignment was stratified by the following:

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

Patients received 3 doses of study drug every 4 weeks up to Treatment Period I (Week 12).

All patients who completed Treatment Period I underwent the second randomization process prior to the study drug administration at Week 12 and entered the Treatment Period II to receive additional 3 doses of study drug every 4 weeks. For the second randomization, patients who were initially randomized to 300 mg of Xolair (Arm 2) were re-randomized in a ratio of 1:1 to switching arm (Arm 2-1) or non-switching arm (Arm 2-2). Patients assigned to switching arm (Arm 2-1) underwent transition to 300 mg of CT-P39 and patients assigned to non-switching arm (Arm 2-2) continued receiving 300 mg of Xolair. Patients who have received 300 mg of CT-P39 (Arm 1) during Treatment Period I maintained receiving 300 mg of CT-P39. Patients who have received 150 mg of CT-P39 (Arm 3) or Xolair (Arm 4) maintained the assigned study drug with an increased dose of 300 mg.

The second randomization was stratified by the following:

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

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

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

The blind could be broken during the study only if specific emergency treatment would dictate as knowing the study drug assignment is required for medical management. The date, time, and reason for the unblinding was to be documented in the appropriate field of the eCRF.

- **Statistical methods**

Analysis Sets

Analysis Subsets for Treatment Period I

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

• Modified Intent-to-Treat (mITT) Set: The mITT Set was defined as all randomly assigned patients who received at least 1 full dose of either of the study drugs during Treatment Period I.

• Per-Protocol (PP) Set: The PP Set was defined as all randomly assigned patients who received all 3 doses of study drug during Treatment Period I and had an ISS7 assessment at Week 12. Patients with a major protocol deviation that might affect the interpretation of study results of primary efficacy endpoint were excluded from the PP Set.

• Pharmacokinetic (PK) Set: The PK Set was defined as all patients who received at least 1 full dose of either of the study drugs during Treatment Period I and had at least 1 post-treatment PK result prior to dosing at Week 12. For any patients found to be noncompliant with respect to dosing, a determination of inclusion into the PK Set was made on a case-by-case basis at the blinded data review meeting.

• Safety Set: The Safety Set was defined as all randomly assigned patients who received at least 1 dose (full or partial) of either of the study drugs.

Analysis Subsets for Treatment Period II

• Randomised Set – Treatment Period II (RAN-TP2) Subset: The RAN-TP2 Subset was defined as all patients in RAN Set who underwent the second randomization regardless of whether they received either of the study drugs during Treatment Period II.

• Modified Intent-to-Treat Set – Treatment Period II (mITT-TP2) Subset: The mITT-TP2 Subset was defined as all patients in the mITT Set who underwent the second randomization and received at least 1 full dose of either of the study drugs during Treatment Period II.

• Pharmacokinetic Set – Treatment Period II (PK-TP2) Subset: The PK-TP2 Subset was defined as all patients in PK Set who received at least 1 full dose of either of the study drugs during Treatment Period II and had at least 1 post-treatment PK result after Week 12.

• Safety Set – Treatment Period II (Safety-TP2) Subset: The Safety-TP2 Subset was defined as all patients in Safety Set who received at least 1 dose (full or partial) of either of the study drugs during Treatment Period II.

Efficacy Analyses

Primary Endpoint:

The primary analysis was summarized using the mITT Set. A supportive analysis was repeated using the PP Set. The difference of least squares means between 300 mg of CT-P39 (Arm 1) and 300 mg of Xolair (Arm 2) in change from baseline in ISS7 at Week 12 was calculated using an analysis of covariance (ANCOVA) model with treatment arm as a fixed effect and baseline ISS7, BW on Day 1 and country as covariates. Statistical equivalence was declared if the two-sided 95% confidence interval (CI) for the treatment difference was entirely within an equivalence margin of [-2.0, 2.0].

In order to evaluate the impact of missing data on the primary endpoint result, sensitivity analysis was performed by tipping point analysis for the mITT Set.

Secondary Endpoints:

Secondary efficacy endpoints were summarized using the mITT Set, PP Set and mITT-TP2 Subset.

Supportive analysis of relative potency of CT-P39 compared to Xolair was summarized. The other secondary endpoints were summarized by treatment arms as appropriate and listed by patient. In case of calculating parameters defining "responder and non-responder", the patient was classified as a non-

responder if a patient had missing weekly scores for the given week. Graphical presentations of data collected at each week was presented for the mITT Set, where applicable.

Pharmacokinetic Analysis

The PK Set and PK-TP2 Subset were used in PK data analyses. Serum concentrations of omalizumab were presented in a listing at each scheduled visit. Pharmacokinetic parameter of C_{trough} was summarized using quantitative descriptive statistics (including geometric mean and coefficient of variation, as appropriate) by treatment and study visit.

Quality of Life Analysis

The mITT Set and mITT-TP2 Subset were used in the analysis of DLQI and CU-Q2oL scores. A supportive analysis was repeated using the PP Set. Overall DLQI and CU-Q2oL scores were summarized using descriptive statistics of actual value and change from baseline at scheduled visits.

Safety Analyses

The Safety Set and Safety-TP2 Subset were used in safety analysis.

Missing Values and Outliers

In general, missing data were imputed unless were in relation to missing daily or weekly ISS, prior and concomitant medications, and adverse events (AEs).

Missing daily or weekly ISS

The weekly score (ISS7, weekly hives severity score [HSS7] and weekly urticaria activity score [UAS7]) is the sum of the average daily scores over 7 days each week. The daily scores were calculated as the average of the morning and evening scores based on daily patient eDiary entries. eDiary entries on or after 24:00 and prior to 6:00 am were considered as evening scores for the previous days. When either the morning or evening score were missing, the non-missing score for that day (morning or evening) were be used as the daily score.

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

- If a patient has at least 4 non-missing daily scores included in the calculation of the weekly score the weekly score was calculated as the sum of the available patient eDiary scores in that week, divided by the number of days that have a non-missing diary score, and then multiplied by 7.
- If there were less than 4 non-missing daily scores included in the calculation of the weekly score, then the weekly score is missing for the week.

To assess the robustness of analysis result, a tipping point approach for comparison of mean change from baseline in ISS7 at Week 12 was be applied, whereby the impact of missing data on the conclusions was be assessed. The tipping points was defined to be the particular setting for the missing values that would change the study's conclusions. Multiple Imputation (MI) under the Missing Not at Random (MNAR) assumption was applied to search for a tipping point by using "shift" approaches until the conclusion is reversed. Imputed values were shifted gradually by treatment groups (CT-P39 300 mg vs. Xolair 300 mg) to make MNAR scenarios. A point estimate and 95% CI for treatment difference was provided using the same analysis method for the primary analysis. The setting where CI no longer rules out differences in the primary endpoint for the therapeutic equivalence margin of [-2.0, 2.0] will be displayed.

Results

- **Participant flow**

A total of 783 patients were screened for the study. Of these, 149 patients were screen failures and were excluded from the study.

A total of 634 patients were randomly assigned to the study drug, and 619 patients were included in the RAN Set excluding the patients from one GCP noncompliant site.

Treatment Period I

A total of 619 patients were randomized for the RAN Set (204 patients in Arm 1, 205 patients in Arm 2, 107 patients in Arm 3, and 103 patients in Arm 4) in the study. All these patients were administered the study drug excluding 1 (0.5%) patient in Arm 1.

Of these, 16 (7.8%) patients in Arm 1, 13 (6.3%) patients in Arm 2, 6 (5.6%) patients in Arm 3, and 5 (4.9%) patients in Arm 4 discontinued the study drug in Treatment Period I. The most common primary reason for study treatment discontinuation was consent withdrawal by patient (7 [3.4%] patients in Arm 1, 6 [2.9%] patients in Arm 2, 4 [3.7%] patients in Arm 3, and 5 [4.9%] patients in Arm 4). The mean (SD) time on study treatment prior to discontinuation in Treatment Period I was 25.5 (27.0) days in Arm 1, 29.4 (23.7) days in Arm 2, 24.7 (27.8) days in Arm 3, and 29.0 (28.0) days in Arm 4.

The proportion of patients who completed Treatment Period I was similar across the treatment arms. During Treatment Period I, 15 (7.4%) patients in Arm 1, 10 (4.9%) patients in Arm 2, 5 (4.7%) patients in Arm 3, and 5 (4.9%) patients in Arm 4 discontinued their study participation.

The most common primary reason for study discontinuation was withdrawal by patient (8 [3.9%] patients in Arm 1, 6 [2.9%] patients in Arm 2, 4 [3.7%] patients in Arm 3, and 5 [4.9%] patients in Arm 4).

Among the patients who discontinued study drug during Treatment Period I, a total of 4 patients (4 [2.0%] patients in Arm 1) discontinued study drug and study participation due to the Ukraine War.

Table 17: Patient Disposition – (RAN Set) – Treatment Period I

	Total (N = 619)
Total number of patients	
Screened[1]	783
Screening failure	149
Primary reason for screening failure[2]	
Inclusion/exclusion criteria not met	83
Patient withdrew consent	42
Other	24
GCP non-compliance site	15

	Arm 1 (N = 204)	Arm 2 (N = 205)	Arm 3 (N = 107)	Arm 4 (N = 103)
	Number (%) of Patients			
Randomized (1st)	204	205	107	103
Administered the study drug in Treatment Period I	203 (99.5%)[3]	205 (100.0%)	107 (100.0%)	103 (100.0%)
Discontinued the study drug in Treatment Period I	16 (7.8%)	13 (6.3%)	6 (5.6%)	5 (4.9%)
Discontinued the study in Treatment Period I	15 (7.4%)	10 (4.9%)	5 (4.7%)	5 (4.9%)
Primary reason for study treatment discontinuation in Treatment Period I				
Consent withdrawal by patient	7 (3.4%)	6 (2.9%)	4 (3.7%)	5 (4.9%)
Patient refusal (but, continuing regular study visit)	1 (0.5%)	1 (0.5%)	1 (0.9%)	0
Disease progression	1 (0.5%)	1 (0.5%)	0	0
Adverse event	3 (1.5%)	2 (1.0%)	0	0
Significant protocol deviation	0	3 (1.5%)	0	0
Pregnancy	0	0	0	0
Investigator decision	0	0	0	0
Lost to follow-up	0	0	1 (0.9%)	0

	Arm 1 (N = 204)	Arm 2 (N = 205)	Arm 3 (N = 107)	Arm 4 (N = 103)
	Number (%) of Patients			
Study terminated by sponsor	0	0	0	0
Other	4 (2.0%)	0	0	0
Time on Study Treatment Prior to Discontinuation in Treatment Period I (days)[4]				
n	16	13	6	5
Mean	25.5	29.4	24.7	29.0
SD	27.0	23.7	27.8	28.0
Minimum	1	1	1	1
Median	14.5	29.0	15.5	29.0
Maximum	63	64	59	57
Primary reason for study termination in Treatment Period I				
Withdrawal by patient	8 (3.9%)	6 (2.9%)	4 (3.7%)	5 (4.9%)
Lost to follow-up	0	0	1 (0.9%)	0
Adverse event	2 (1.0%)	1 (0.5%)	0	0
Investigator's decision	0	2 (1.0%)	0	0
Study terminated by sponsor	0	0	0	0
Other	5 (2.5%)	1 (0.5%)	0	0

Abbreviations: Arm 1 = CT-P39 300 mg; Arm 2 = Xolair 300 mg; Arm 3 = CT-P39 150 mg; Arm 4 = Xolair 150 mg; n = Number of patients; N = Total number of patients; RAN = Randomized; SD = Standard deviation.

[1] This included screening failures and randomized patients including GCP non-compliance sites.

[2] This summary included screening failures only.

[3] One patient [redacted] in Arm 1 who was randomized by mistake terminated the study prior to the first study drug administration.

[4] Only for patients who initiated the study treatment during each treatment period and were prematurely discontinued from study treatment calculated as (Date of last administration – Date of first administration in each period +1).

Treatment Period II

A total of 579 patients underwent the second randomisation process prior to the study drug administration at Week 12 (187 [100.0%] patients in Arm 1, 96 [100.0%] patients in Arm 2-1, 97 [100.0%] patients in Arm 2-2, 101 [100.0%] patients in Arm 3, and 98 [100.0%] patients in Arm 4). All of these patients were administered the study drug in Treatment Period II except 1 (1.0%) patient in Arm 2-2.

Of these, 6 (3.2%) patients in Arm 1, 2 (2.1%) patients in Arm 2-1, 2 (2.1%) patients in Arm 2-2, 2 (2.0%) patients in Arm 3, and 4 (4.1%) patients in Arm 4 discontinued the study drug in Treatment Period II. The most common primary reason for study treatment discontinuation was consent withdrawal by patient (3 [1.6%] patients in Arm 1, 1 [1.0%] patient in Arm 2-1, 1 [1.0%] patient in Arm 3, and 2 [2.0%] patients in Arm 4). The mean (SD) time on study treatment prior to discontinuation in Treatment Period II was 10.0 (14.0) days in Arm 1, 14.0 (18.4) days in Arm 2-1, 1.0 (0.0) day in Arm 2-2, 1.0 (0.0) day in Arm 3, and 17.0 (18.6) days in Arm 4.

The proportion of patients who completed Treatment Period II was similar between all treatment arms. During Treatment Period II, 6 (3.2%) patients in Arm 1, 3 (3.1%) patients in Arm 2-1, 2 (2.1%) patients in Arm 2-2, 3 (3.0%) patients in Arm 3, and 3 (3.1%) patients in Arm 4 discontinued their study participation. The most common primary reason for study discontinuation was withdrawal by patient (4 [2.1%] patients in Arm 1, 2 [2.1%] patients in Arm 2-1, 2 [2.0%] patients in Arm 3, and 2 [2.0%] patients in Arm 4). Among the patients who discontinued the study drug during Treatment Period II, 1 (1.0%) patient in Arm 2-1 discontinued the study drug and study participation due to the Ukraine War.

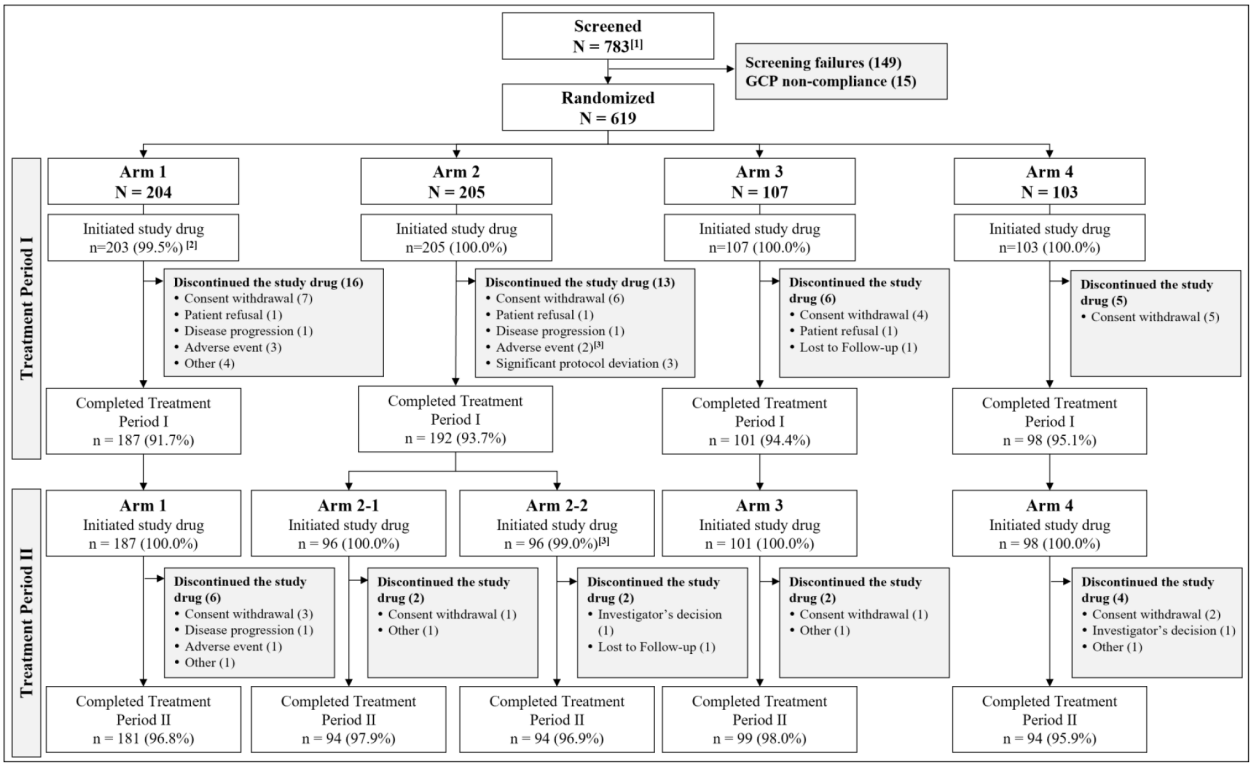


Figure 6. Patient Disposition

- **Recruitment**

Study Initiation Date: 09 December 2020 (first patient randomly assigned to treatment)
Study Completion Date: 12 January 2023 (Last Patient Week 24 Visit)

- **Conduct of the study**

Changes in the Conduct of the Study Related to the War in Ukraine

Due to the war in Ukraine that occurred during the study, increase in protocol deviations was unavoidable. To protect the patient's right and safety with continuation of treatment as well as to preserve the quality of the data, the Sponsor implemented the following alternative measures:

- Temporary use of local laboratories: Since the courier service was not available for laboratory sample pick up and shipment to the central laboratory was also not possible, Sponsor agreed that sites should use the local laboratories for ambient sample tests and the frozen samples to be stored at the sites until those can be shipped to the central laboratory. Electronic CRF was updated to include local laboratory data.
- Changes in the site monitoring visits: The site was designed for onsite site monitoring visits with 100% source data verification for critical data. Considering the critical situation and the temporary travel restrictions due to the critical situation in Ukraine, remote visits with remote source data verification were approved. The CRAs and sites were trained on the processes and accesses were granted to CRAs and site staff for the secure portal where the source documents were uploaded.
- Adaptation of remote visits in the follow-up period: Due to the travel restrictions Sponsor implemented the possibility for remote (phone) visits for patients during the follow up visits. In case a patient was unable to visit the site due to relocation etc. the follow-up visit was performed over the phone and the collected data were documented in the source documents and transcribed into the eCRF.

- H1-antihistamine was supplied by the sponsor via a third-party vendor.
- The study monitoring plan was updated to implement an emergency plan to allow remote source data verification in case of site visit restrictions due to disruption in Ukraine. Guidance document on the study conduct was prepared and distributed to the sites in Ukraine.

Protocol Amendments
The original protocol dated 24 June 2020 was amended 11 times, where 4 were global protocol amendments and 7 were country-specific protocol amendments. Country-specific amendments numbered as A.X is country-specific version for US, and B.X is for Republic of Korea.
Brief summaries of the non-administrative changes in all protocol amendments are outlined below.

Version 2.0 Dated 31 August 2020
• A secondary efficacy endpoint 'Change from baseline in number of tablets/week of rescue therapy at Weeks 8, 12, and 24' was added to address a possible imbalance in rescue therapy use between the treatment arms.
• A patient was allowed to take additional H1-antihistmaine in case a patient discontinued the study drug during the study treatment periods.
• A patient had to return to the study center by regular scheduled time intervals even if a patient discontinued the study drug during the treatment period to apply treatment policy estimand.
• The following statement "Back-up samples for PK, immunogenicity, and free IgE will be retained at the central laboratory as a back-up and blood samples for free IgE assessments can be used for additional analysis for either free or total IgE" was added.
• History of and/or concomitant myocardial infarction' was added to exclusion criteria considering myocardial infarction is specified as contraindications in Korea Ministry Food and Drug Safety label.

Version 2.0, Including Country Specific A.0 Dated 31 August 2020
• 'Relative potency' was included in primary endpoint analysis according to FDA BPD Type 2 preliminary response.
• Co-primary evaluations of the primary endpoint were added to clarify primary endpoint evaluation method.
• Missing data imputation method was explained to impute missing values for ISS7 at Week 12.
• Statistical power, 2 one-sided 5% significance level and an equivalence margin were changed from 83%, 2.5%, and [-2.0, +2.0] to 95%, 5%, and [-2.5, +2.0], respectively to relax the lower bound of the equivalence margin according to FDA BPD Type 2 preliminary response.
• 'Comparison of the Mean Change from baseline in ISS7 of 300 mg Arms at Week 12' was added to explain primary endpoint analysis.
• 'For AESIs, the incidence rate and its difference between treatment arms were presented along with their 95% CI' was added.

Version 2.1 Dated 03 September 2020
• Details of analytical facilities was referred to the ICF instead of containing those details in the protocol. This change was done to prevent the protocol to be amended each time laboratory information is updated.

Version 2.1, Including Country Specific B.0 Dated 17 September 2020
• The sentences stating that countries may pooled into a region for covariate in statistical models were added to according to Ministry of Food and Drug Safety comment.

Version 2.1, including country specific B.1 dated 06 October 2020
Below country-specific changes additionally applied compared to the previous country-specific version:
• Multiple imputation method was added to explain multiple imputation for missing data.
• Protocol deviations section was updated to explain major deviations.

Version 2.2 Dated 04 November 2020
• Immunogenicity timepoint was added to Weeks 4, 8, 16, and 20 to reflect FDA's comment.

• 'Benefits and risk assessment and risk mitigation for COVID-19' was added in accordance with Polish Ministry of Health.
• Approval of omalizumab for the treatment of chronic rhinosinusitis with nasal polyps in Europe was updated.

Version 2.2, Including Country Specific A.0 and Version 2.2, Including Country Specific B.0 Dated 17 November 2020.
There were no additional country-specific changes compared to version 2.0, A.0 and version 2.1, B.1, respectively.

Version 2.3 Dated 10 August 2021
• The start time of background medication was changed to at least 3 days before start recording the baseline ISS7 which was the earliest valid efficacy data.
• Risk assessment for concomitant use of a COVID-19 vaccine during the study was added.
• 'Patient missed at least 1 dose before Week 12' was deleted from the study treatment discontinuation reason.
• It was changed to allow the patients who showed positive result of antibody test due to the past hepatitis C infection to be enrolled in the study.
• The description of conversion method for calculating rescue medications was added.

Changes in the Conduct of the Study Related to Risk Management
During the risk-based monitoring, as an action for exceeding the QTL of 'High number of patients noncompliant with ISS7 at Week 12', the targeted sample size was increased to 624 patients in total to secure 80% of power in primary analysis. Finally, 634 patients were enrolled in the study beyond the planned sample size.

Changes to the Planned Analyses
The following were the changes to analyses from the protocol:
• Section 7.4.3.1 and 7.4.3.2 of the protocol (version 2.3 dated 10 August 2021 stated that individual domain scores and overall scores of DLQI and CU-Q2oL were summarised. Since individual scores had a significant clinical meaning when they were integrated into the overall scale, only overall scores were summarized.
• Section 7.4.4 of the protocol (version 2.3 dated 10 August 2021 stated that serum concentrations of omalizumab and C_{trough} were summarised. Since each PK blood sampling was scheduled right before the study drug administration, C_{trough} was the same as the concentration right before the study drug administration.
Therefore, the serum concentration was summarized as C_{trough}.

Protocol deviations:

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

Major protocol deviations are defined as deviation that may affect the interpretation of study results or the patient's rights, safety, or welfare.

There was a significant GCP non-compliance found at one site during the study. A total of 15 patients from the site (7 patients in Arm 1, 5 patients in Arm 2, 1 patient in Arm 3, and 2 patients in Arm 4) were excluded from all the analysis sets.

Other major protocol deviations which affected primary efficacy result were non-adherence to inclusion/exclusion criteria (1 patient in Arm 1, 7 patients in Arm 2, and 2 patients in Arm 3) and receipt of prohibited medication (1 patient each in Arm 1, Arm 2, and Arm 4).

Table 18: Major Protocol Deviations – (All Randomly Assigned Patients)

	Arm 1 (N = 211)	Arm 2 (N = 210)	Arm 3 (N = 108)	Arm 4 (N = 105)
	Number (%) of Patients			
Major protocol deviation				
Significant GCP non-compliance	7	5	1	2
Non-adherence to I/E criteria which affect efficacy result	1	7	2	0
Receipt of prohibited medication	1	1	0	1

Abbreviations: Arm 1 = CT-P39 300 mg; Arm 2 = Xolair 300 mg (re-randomized to switching arm and non-switching arm after Week 12); Arm 3 = Dose increased from CT-P39 150 mg to 300 mg after Week 12; Arm 4 = Dose increased from Xolair 150 mg to 300 mg after Week 12; GCP = Good Clinical Practice; I/E = Inclusion or exclusion criteria; N = Total number of patients.

Note: All randomly assigned patients included patients from GCP non-compliance sites.

- **Baseline data**

Treatment Period I

The demographic characteristics were similar between the 4 treatment arms. The median (min, max) age of patients was 43.0 (15, 71) years in Arm 1, 41.0 (12, 75) years in Arm 2, 42.0 (13, 75) years in Arm 3, and 42.0 (13, 72) years in Arm 4. The proportion of males and females were similar between the treatment arms. The mean (SD) BMI of patients at screening was 26.728 (5.349) kg/m2 in Arm 1, 27.225 (5.353) kg/m2 in Arm 2, 26.384 (5.463) kg/m2 in Arm 3, and 26.354 (5.441) kg/m2 in Arm 4. Majority of the patients across the treatment arms were white (500 [80.8%] patients) and non-Hispanic or non-Latino (618 [99.8%] patients). 65 (31.9%) patients in Arm 1, 70 (34.1%) patients in Arm 2, 27 (25.2%) patients in Arm 3, and 40 (38.8%) patients in Arm 4 had presence of angioedema at baseline.

Overall, stratification factors were generally similar across the treatment arms for the RAN Set.

The majority (ranged from 79.5% to 83.5% across treatment arms) of the patients had baseline ISS7 of ≥13 points. There was a similar percentage of patients enrolled in each country and body weight category across the 4 treatment arms.

Table 19: Demographics and Stratification Details – (RAN Set) – Treatment Period I

	Arm 1 (N = 204)	Arm 2 (N = 205)	Arm 3 (N = 107)	Arm 4 (N = 103)
Age (years)				
n	204	205	107	103
Mean	43.2	42.9	42.9	41.5
SD	13.3	13.7	15.0	13.8
Minimum	15	12	13	13
Median	43.0	41.0	42.0	42.0
Maximum	71	75	75	72
Gender, n (%)				
Male	71 (34.8%)	74 (36.1%)	40 (37.4%)	31 (30.1%)
Female	133 (65.2%)	131 (63.9%)	67 (62.6%)	72 (69.9%)
Angioedema presence, n (%)				
Yes	65 (31.9%)	70 (34.1%)	27 (25.2%)	40 (38.8%)
No	134 (65.7%)	131 (63.9%)	80 (74.8%)	62 (60.2%)
Stratification factors				
Baseline ISS7, n (%)				
< 13 points	36 (17.6%)	42 (20.5%)	20 (18.7%)	17 (16.5%)
≥ 13 points	168 (82.4%)	163 (79.5%)	87 (81.3%)	86 (83.5%)
Weight on Day 1, n (%)				
< 80 kg	123 (60.3%)	125 (61.0%)	65 (60.7%)	65 (63.1%)
≥ 80 kg	81 (39.7%)	80 (39.0%)	42 (39.3%)	38 (36.9%)
Country, n (%)				
Bulgaria	40 (19.6%)	42 (20.5%)	23 (21.5%)	20 (19.4%)
Greece	3 (1.5%)	1 (0.5%)	1 (0.9%)	1 (1.0%)
Hungary	1 (0.5%)	2 (1.0%)	2 (1.9%)	1 (1.0%)
Korea	38 (18.6%)	40 (19.5%)	21 (19.6%)	20 (19.4%)
Poland	87 (42.6%)	87 (42.4%)	43 (40.2%)	45 (43.7%)
Ukraine	35 (17.2%)	33 (16.1%)	17 (15.9%)	16 (15.5%)

Abbreviations: Arm 1 = CT-P39 300 mg; Arm 2 = Xolair 300 mg; Arm 3 = CT-P39 150 mg; Arm 4 = Xolair 150 mg; ISS7 = Weekly Itch Severity Score; n = Number of patients; N = Total number of patients; RAN = Randomized; SD = Standard deviation.

[1] Percentages were calculated by using the number of female patients.

Treatment Period II

Overall, demographic characteristics for the RAN-TP2 Subset showed a similar trend with those of the RAN Set in all treatment arms. There was no notable difference in demographic characteristics and stratification details between the 5 treatment arms for Treatment Period II.

Table 20: Demographics and Stratification Details – (RAN- TP2 Subset) – Treatment Period II

	Arm 1 (N = 187)	Arm 2-1 (N = 96)	Arm 2-2 (N = 97)	Arm 3 (N = 101)	Arm 4 (N = 98)
Age (years)					
n	187	96	97	101	98
Mean	43.4	42.5	42.8	42.6	41.2
SD	13.2	12.8	14.3	14.7	13.9
Minimum	15	13	12	13	13
Median	43.0	41.0	40.0	42.0	41.0
Maximum	71	69	75	75	72
Gender, n (%)					
Male	63 (33.7%)	31 (32.3%)	41 (42.3%)	36 (35.6%)	31 (31.6%)
Female	124 (66.3%)	65 (67.7%)	56 (57.7%)	65 (64.4%)	67 (68.4%)
Stratification factors					
Decrease from baseline in ISS7 at Week 12, n (%)					
< 5 points	44 (23.5%)	21 (21.9%)	17 (17.5%)	24 (23.8%)	29 (29.6%)
≥ 5 points	143 (76.5%)	75 (78.1%)	80 (82.5%)	77 (76.2%)	69 (70.4%)
Weight at Week 12, n (%)					
< 80 kg	114 (61.0%)	57 (59.4%)	58 (59.8%)	63 (62.4%)	61 (62.2%)
≥ 80 kg	73 (39.0%)	39 (40.6%)	39 (40.2%)	38 (37.6%)	37 (37.8%)

Abbreviations: Arm 1 = CT-P39 300 mg Maintenance; Arm 2-1 = Switched from Xolair to CT-P39 300 mg after Week 12; Arm 2-2 = Xolair 300 mg Maintenance; Arm 3 = Dose increased from CT-P39 150 mg to 300 mg after Week 12; Arm 4 = Dose increased from Xolair 150 mg to 300 mg after Week 12; ISS7 = Weekly Itch Severity Score; n = Number of patients; N = Total number of patients; RAN = Randomized; SD = Standard deviation; TP2 = Treatment Period II.

[1] Percentages were calculated by using the number of female patients.

Other Baseline Characteristics

Viral Serology

Except for 2 patients, all other patients tested for viral serology at screening visit were identified not to be infected with hepatitis B, hepatitis C, and HIV for the RAN Set.

During the Screening Period, 2 patients reported HBsAg and HIV positive result each. One patient in Arm 3 had a positive result for HBsAg test and it was reported as a deviation of noncompliance with exclusion criteria #3. The patient had ongoing medical history of chronic hepatitis B, however, no TEAEs related to HBV infection were reported in this patient during the study participation. One patient in Arm 2 had positive HIV from the screening period but was randomized without confirmation of the result. The event was reported as an AE of HIV disease as it was identified during the Screening Period. Due to this protocol deviation, the patient discontinued study treatment and study participation after Week 4 administration.

No further patients were identified as being infected with hepatitis B, hepatitis C, or HIV during the study.

Prior Medications

All patients had taken at least 1 prior medication for the Safety Set. The most common prior medication by drug class was antihistamines for systemic use (203 [100.0%] patients in Arm 1, 205 [100.0%] patients in Arm 2, 107 [100.0%] patients in Arm 3, and 103 [100.0%] patients in Arm 4) in line with the inclusion criteria 3-a of the symptom persistence despite use of H1-antihistamines. The second common prior medication was corticosteroids for systemic use (69 [34.0%] patients in Arm 1,

78 [38.0%] patients in Arm 2, 39 [36.4%] patients in Arm 3, and 41 [39.8%] patients in Arm 4) followed by corticosteroids, dermatological preparations (21 [10.3%] patients in Arm 1, 15 [7.3%] patients in Arm 2, 9 [8.4%] patients in Arm 3, and 7 [6.8%] patients in Arm 4).

Concomitant Medications
All patients were allowed to take pre-defined nonsedating H1-antihistamines at approved dose throughout the study. In addition to being used as background medication, it was allowed as rescue therapy for itch relief on an as-needed basis throughout the study. The medication of nonsedating H1-antihistamines, used as background medication and rescue therapy were separately recorded and evaluated.

Background nonsedating H1-antihistamine treatment
All patients maintained the same background nonsedating H1-antihistamine during the study except 1 patient (; Arm 4) who switched to another background nonsedating H1-antihistamine during Treatment Period II. The most common background nonsedating H1-antihistamine was bilastine (ranged from 31.7% to 37.4% patients across the treatment arms) followed by levocetirizine dihydrochloride (ranged from 19.5% to 28.1% patients across the treatment arms) for the Safety Set.

During Treatment Period I, there were no patients who had taken additional nonsedating H1-antihistamines in addition to the background nonsedating H1-antihistamine for the Safety Set. During Treatment Period II, a total of 6 (3.2%) patients in Arm 1, 2 (2.1%) patients in Arm 2-1, 2 (2.1%) patients in Arm 2-2, 2 (2.0%) patients in Arm 3, and 2 (2.0%) patients in Arm 4 had taken at least 1 additional nonsedating H1-antihistamine in addition to the background nonsedating H1-antihistamine for the Safety-TP2 Subset. All of them had initiated additional H1-antihistamine therapy from the EOT visit.

Rescue Therapy
Another nonsedating H1-antihistamine, in addition to being used as background medication, was allowed as rescue therapy for itch relief on an as-needed basis throughout the study. The selection of the rescue therapy could be made once for an individual patient among the regimens pre-defined in the protocol.

All patients maintained the same rescue medication during the study except for 2 patients who switched their rescue medication (one patient in Arm 2-1, and one patient in Arm 4). The most commonly selected rescue therapy was bilastine (ranged from 25.2% to 29.3% patients across the treatment arms) followed by rupatadine (ranged from 13.1% to 24.3% patients across the treatment arms) for the Safety Set. Similar trend was observed in the Safety-TP2 Subset.

- **Numbers analysed**

Table 21: Analysis Sets – (RAN Set)

	Arm 1 (N = 204)	Arm 2 (N = 205)	Arm 3 (N = 107)	Arm 4 (N = 103)
	Number (%) of Patients			
RAN Set	204	205	107	103
mITT Set	203 (99.5%)	205 (100.0%)	107 (100.0%)	103 (100.0%)
PP Set	179 (87.7%)	183 (89.3%)	99 (92.5%)	93 (90.3%)
PK Set	199	204	105	102
Safety Set	203	205	107	103

Abbreviation: Arm 1 = CT-P39 300 mg; Arm 2 = Xolair 300 mg; Arm 3 = CT-P39 150 mg; Arm 4 = Xolair 150 mg; N = Total number of patients; mITT = Modified Intent-to-Treat, PK = Pharmacokinetic, PP = Per-protocol, RAN = Randomized.
Note: There were no mis-randomized patients. Thus, there were no discrepancies between the treatment the patients actually received and the treatment arm assigned from randomization.

- **Outcomes and estimation**

Primary endpoint

Change from Baseline in Weekly Itch Severity Score of 300 mg of CT-P39 (Arm 1) and 300 mg of Xolair (Arm 2) at Week 12

The LS mean (SE) change from baseline in ISS7 at Week 12 was -9.21 (0.796) points in CT-P39 300 mg treatment arm (Arm 1) and -9.98 (0.798) points in Xolair 300 mg treatment arm (Arm 2) for the mITT Set (estimate of treatment difference: 0.77). The 95% CI of treatment difference in the mean change from baseline in ISS7 at Week 12 between 300 mg of CT-P39 and 300 mg of Xolair treatment arms was [-0.37, 1.90] for the mITT Set and entirely within the equivalence margin of [-2.0, 2.0] which demonstrated the therapeutic equivalence between CT-P39 and Xolair.

For the PP Set, similar result to that of the mITT Set was reported. The 95% CI of treatment difference in the mean change from baseline in ISS7 at Week 12 between 300 mg of CT-P39 and 300 mg of Xolair was [-0.45, 1.84] for the PP Set and also within the equivalence margin of [-2.0, 2.0], which supported the result of the primary analysis.

Table 22: Statistical Analysis of Mean Change from Baseline in Weekly Itch severity Score at Week 12 (ANCOVA) – (mITT and PP Set)

Treatment	n	LS Mean (SE)	Estimate of Treatment Difference	95% CI of Treatment Difference
mITT Set				
CT-P39 300 mg (Arm 1)	186	-9.21 (0.796)	0.77	[-0.37, 1.90]
Xolair 300 mg (Arm 2)	192	-9.98 (0.798)		
PP Set				
CT-P39 300 mg (Arm 1)	179	-9.48 (0.790)	0.69	[-0.45, 1.84]
Xolair 300 mg (Arm 2)	183	-10.17 (0.792)		

Abbreviations: ANCOVA = Analysis of covariate; CI = Confidence interval; LS = Least squares; mITT = Modified Intent-to-Treat; n = Number of patients; PP = Per-protocol; SE = Standard error.
Note: An ANCOVA was performed with the treatment as a fixed effect and baseline ISS7, body weight on Day 1 and country as covariates.

Sensitivity Analysis

Tipping point analysis evaluated the impact of the missing data by shifting imputed value of change from baseline of ISS7 at Week 12 gradually by unit of 1 point in ISS7 from each imputed value from multiple imputation.

The number of patients with missing value in change from baseline in ISS7 at Week 12 for 300 mg treatment arms were 30 patients and distributed similarly between CT-P39 300 mg treatment arm (Arm 1) and Xolair 300 mg treatment arm (Arm 2) (17 [8.4%] patients in Arm 1 and 13 [6.3%] patients in Arm 2). For the result imputed using the approach of multiple imputation (i.e., no shift), 95% CI of treatment difference in the mean change from the baseline at Week 12 between 300 mg of CT P39 and 300 mg of Xolair was [-0.40, 1.81] for the mITT Set and entirely within the equivalence margin of [-2.0, 2.0], supporting the therapeutic equivalence between CT-P39 and Xolair shown in the primary analysis. The therapeutic equivalence between CT-P39 and Xolair was demonstrated, when shifting the imputed value of change from baseline at Week 12 for CT-P39 300 mg treatment arm before +3 units while there was no shift in Xolair 300 mg treatment arm.

The result of multiple imputation and tipping point analysis showed that missing data had no major impact on the result for the primary efficacy endpoint, which supported the therapeutic equivalence between CT-P39 and Xolair from the primary analysis result.

Secondary Efficacy Endpoints

Relative Potency of CT-P39 Compared with Xolair as Determined by Change from Baseline in Weekly Itch Severity Score at Week 12

Relative potency of CT-P39 compared with Xolair as determined by change from baseline in ISS7 at Week 12 was to be tested for the mITT Set and PP Set, however, statistically valid relative potency and its CI could not be calculated as the assumptions of the parallel-line assay were not satisfied, which are the prerequisites for determination of relative potency.

Change from Baseline in Weekly Itch Severity Score at Weeks 8, 12, and 24

Treatment Period I
The mean ISS7 gradually decreased from the baseline in all treatment arms throughout Treatment Period I.
For the dose level of 300 mg, the mean (SD) changes from baseline in ISS7 were -8.31 (6.29) points in Arm 1 and -9.21 (6.27) points in Arm 2 at Week 8 and -9.31 (6.20) points in Arm 1 and -9.99 (6.18) points in Arm 2 at Week 12 for the mITT Set. Although there were the slight fluctuations by timepoints, the mean (SD) changes from baseline in ISS7 were comparable between Arm 1 and Arm 2 during Treatment Period I.

For the dose level of 150 mg, the mean (SD) changes from baseline in ISS7 were -8.33 (6.13) points in Arm 3 and -7.63 (5.83) points in Arm 4 at Week 8 and -9.56 (5.87) points in Arm 3 and -8.73 (6.65) points in Arm 4 at Week 12 for the mITT Set. For the PP Set, similar result to that of the mITT Set was reported.

Treatment Period II

During Treatment Period II, the mean (SD) changes from baseline in ISS7 at Week 24 were similar among Arm 1, Arm 2-1, and Arm 2-2 (-11.24 [6.23] points in Arm 1, -12.24 [5.69] points in Arm 2-1, and -11.19 [5.88] points in Arm 2-2) for the mITT-TP2 Subset, which indicated that reduction in ISS7 after a single transition from Xolair to CT-P39 was not different from those of patients maintained on CT-P39 or Xolair.

In Arm 3 and Arm 4, in which dose increased from 150 mg to 300 mg, the mean (SD) changes from baseline in ISS7 at Week 24 were -11.76 (5.61) points and -10.69 (6.16) points, respectively, for the mITT-TP2 Subset.

Table 23: Descriptive Statistics for Actual Result and Change from Baseline in Weekly Itch Severity Score – (mITT Set) –Treatment Period I

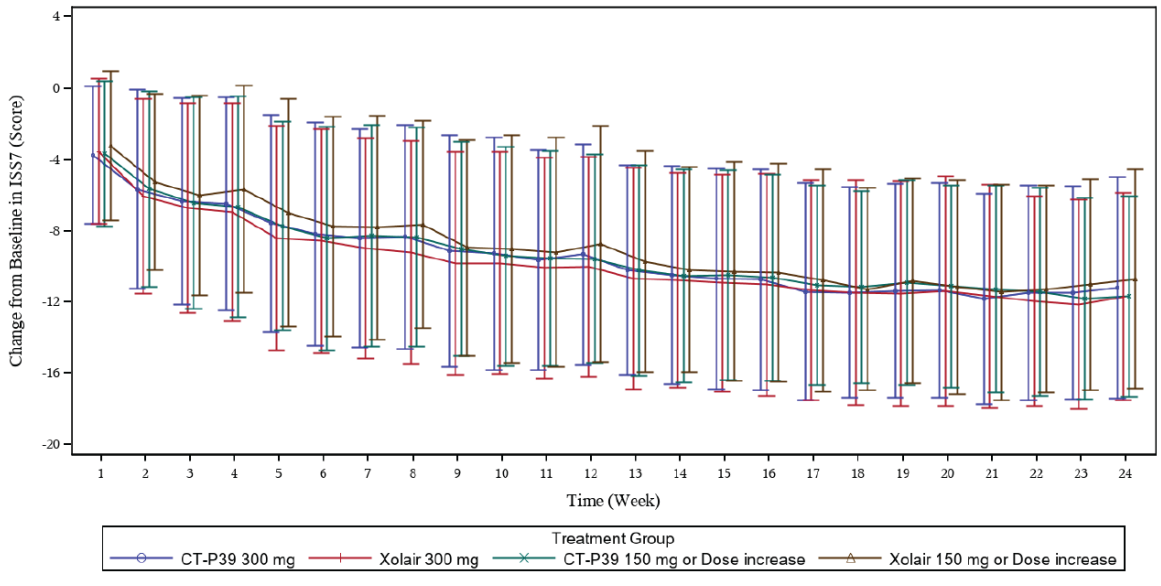
Study Week / Statistics	Arm 1 (N = 203)		Arm 2 (N = 205)		Arm 3 (N = 107)		Arm 4 (N = 103)	
	Actual Result	Change from Baseline	Actual Result	Change from Baseline	Actual Result	Change from Baseline	Actual Result	Change from Baseline
Baseline								
n	203	-	205	-	107	-	103	-
Mean	15.68	-	15.27	-	15.53	-	15.75	-
SD	3.64	-	3.86	-	3.30	-	3.26	-
Minimum	1.8	-	0.0	-	9.0	-	8.5	-
Median	15.50	-	15.00	-	14.50	-	15.00	-
Maximum	21.0	-	21.0	-	21.0	-	21.0	-
Week 4								
n	198	198	201	201	102	102	99	99
Mean	9.11	-6.47	8.27	-6.94	8.97	-6.64	10.09	-5.64
SD	6.30	5.99	5.75	6.12	6.40	6.20	5.86	5.81
Minimum	0.0	-21.0	0.0	-21.0	0.0	-21.0	0.0	-18.0
Median	8.00	-6.19	8.00	-6.50	8.50	-7.00	10.00	-6.00
Maximum	21.0	5.5	21.0	11.5	21.0	7.0	21.0	5.0
Week 8								
n	190	190	195	195	101	101	95	95
Mean	7.19	-8.31	6.16	-9.21	7.26	-8.33	8.15	-7.63
SD	6.16	6.29	5.62	6.27	5.97	6.13	5.59	5.83
Minimum	0.0	-21.0	0.0	-21.0	0.0	-21.0	0.0	-21.0
Median	7.00	-9.00	7.00	-9.00	7.00	-8.00	8.50	-8.00
Maximum	21.0	9.8	21.0	7.0	21.0	4.5	21.0	2.5
Week 12								
n	186	186	192	192	101	101	94	94
Mean	6.18	-9.31	5.33	-9.99	5.87	-9.56	7.08	-8.73
SD	5.98	6.20	5.39	6.18	5.40	5.87	6.15	6.65
Minimum	0.0	-21.0	0.0	-21.0	0.0	-21.0	0.0	-21.0
Median	6.25	-10.50	5.38	-10.00	6.30	-9.50	7.00	-9.25
Maximum	21.0	5.5	21.0	9.5	21.0	4.1	21.0	5.5

Abbreviations: Arm 1 = CT-P39 300 mg; Arm 2 = Xolair 300 mg; Arm 3 = CT-P39 150 mg; Arm 4 = Xolair 150 mg; mITT = Modified Intent-to-Treat; n = Number of patients; N = Total number of patients; SD = Standard deviation.

Table 24: Descriptive Statistics for Actual Result and Change from Baseline in Weekly Itch Severity Score – (mITT-TP2 Subset) –Treatment Period II

Study Week Statistics	Arm 1 (N = 187)		Arm 2-1 (N = 96)		Arm 2-2 (N = 96)		Arm 3 (N = 101)		Arm 4 (N = 98)	
	Actual Result	Change from Baseline	Actual Result	Change from Baseline	Actual Result	Change from Baseline	Actual Result	Change from Baseline	Actual Result	Change from Baseline
Baseline										
n	187	-	96	-	96	-	101	-	98	-
Mean	15.44	-	15.31	-	15.36	-	15.44	-	15.77	-
SD	3.60	-	3.63	-	3.54	-	3.29	-	3.22	-
Minimum	1.8	-	5.0	-	7.5	-	9.0	-	8.5	-
Median	15.00	-	14.50	-	15.00	-	14.50	-	15.00	-
Maximum	21.0	-	21.0	-	21.0	-	21.0	-	21.0	-
Week 24										
n	169	169	88	88	82	82	90	90	86	86
Mean	4.13	-11.24	2.91	-12.24	4.23	-11.19	3.89	-11.76	4.92	-10.69
SD	5.51	6.23	4.75	5.69	5.14	5.88	5.45	5.61	5.49	6.16
Minimum	0.0	-21.0	0.0	-21.0	0.0	-21.0	0.0	-21.0	0.0	-21.0
Median	1.00	-12.50	0.00	-13.25	2.00	-11.83	0.75	-13.95	3.00	-11.75
Maximum	21.0	5.5	21.0	6.5	21.0	9.0	21.0	2.0	21.0	6.5

Abbreviations: Arm 1 = CT-P39 300 mg Maintenance; Arm 2-1 = Switched from Xolair to CT-P39 300 mg after Week 12; Arm 2-2 = Xolair 300 mg Maintenance; Arm 3 = Dose increased from CT-P39 150 mg to 300 mg after Week 12; Arm 4 = Dose increased from Xolair 150 mg to 300 mg after Week 12; mITT = Modified Intent-to-Treat; n = Number of patients; N = Total number of patients; SD = Standard deviation; TP2 = Treatment Period II.



Note: mITT=modified Intent-To-Treat, SD = Standard Deviation, ISS7 = Weekly Itch Severity Score.

Figure 7. Mean (± SD) Plot of Change from Baseline in ISS7

The additional post-hoc analysis of the Mean Change from Baseline in ISS7 were provided with responses to day 120 questions**.**

Table 25: Statistical Analysis of Mean Change from Baseline in ISS7 at Weeks 6, 8, 10, and 12 (ANCOVA) in Study CT-P39 3.1: mITT Set

Timepoint (Study Week)	CT-P39 300 mg (N = 203)	Xolair 300 mg (N = 205)
Week 6		
n	194	196
LS Mean (SE)	-7.58 (0.822)	-8.06 (0.827)

Timepoint (Study Week)	CT-P39 300 mg (N = 203)	Xolair 300 mg (N = 205)
Estimate of Treatment Difference (95% CI)	0.48 (-0.68, 1.64)	
Week 8		
n	190	195
LS Mean (SE)	-7.89 (0.811)	-8.81 (0.815)
Estimate of Treatment Difference (95% CI)	0.92 (-0.23, 2.07)	
Week 10		
n	187	195
LS Mean (SE)	-9.52 (0.859)	-10.10 (0.857)
Estimate of Treatment Difference (95% CI)	0.58 (-0.57, 1.73)	
Week 12		
n	186	192
LS Mean (SE)	-9.21 (0.796)	-9.98 (0.798)
Estimate of Treatment Difference (95% CI)	0.77 (-0.37, 1.90)	

Abbreviations: CI, Confidence interval; ISS7, Weekly itch severity score; LS, Least squares; mITT, Modified intent-to-treat; n, Number of patients; SE, Standard error

Note: An ANCOVA is performed with the treatment as a fixed effect and baseline ISS7, body weight on Day 1 and country as covariates.

Table 26: Statistical Analysis of Change from Baseline in ISS7 Between the 2 Dose Levels in Each Treatment at Weeks 6, 8, 10, and 12 (ANCOVA) (mITT Set)

	CT-P39		Xolair	
	CT-P39 300 mg (N = 203)	CT-P39 150 mg (N = 107)	Xolair 300 mg (N = 205)	Xolair 150 mg (N = 103)
Mean Change from Baseline in ISS7 at Week 6				
N	194	100	196	98
LS Mean (SE)	-7.12 (0.848)	-7.39 (0.919)	-9.29 (0.927)	-8.18 (1.001)
Difference (95% CI)	0.27 (-1.17, 1.72)		-1.10 (-2.48, 0.28)	
Mean Change from Baseline in ISS7 at Week 8				
N	190	101	195	95
LS Mean (SE)	-6.66 (0.836)	-6.74 (0.904)	-9.58 (0.900)	-7.71 (0.974)
Difference (95% CI)	0.08 (-1.34, 1.51)		-1.86 (-3.22, -0.51)	
Mean Change from Baseline in ISS7 at Week 10				
N	187	99	195	97
LS Mean (SE)	-8.22 (0.879)	-8.36 (0.934)	-10.08 (0.912)	-8.95 (0.984)
Difference (95% CI)	0.14 (-1.28, 1.56)		-1.13 (-2.49, 0.23)	
Mean Change from Baseline in ISS7 at Week 12				
N	186	101	192	94
LS Mean (SE)	-7.79 (0.807)	-8.19 (0.869)	-10.73 (0.927)	-9.08 (1.004)
Difference (95% CI)	0.40 (-0.97, 1.78)		-1.65 (-3.05, -0.25)	

Abbreviations: ANCOVA, Analysis of covariate; CI, Confidence Interval; ISS7, Weekly itch severity score; LS, Least squares; mITT, Modified intent-to-treat; N, Total number of patients; n, Number of patients; SE, Standard error

Note: An ANCOVA is performed with the treatment as a fixed effect and baseline ISS7, body weight on Day 1 and country as covariates.

Time to Minimally Important Difference (Reduction of ≥ 5 Points from Baseline) Response in Weekly Itch Severity Score by Week 12

The proportions of responders achieving MID response in ISS7 by Week 12 were similar between 300 mg treatment arms (173 [85.2%] patients in Arm 1 and 173 [84.4%] patients in Arm 2) for the mITT Set. Median times (95% CI) to achieve first MID response in ISS7 by Week 12 were the same between 300 mg treatment arms (2.00 [2.00, 3.00] weeks in both Arm 1 and Arm 2) for the mITT Set.
The proportions of responders achieving MID response in ISS7 by Week 12 were 88 (82.2%) patients in Arm 3 and 87 (84.5%) patients in Arm 4 for the mITT Set. Also, in both Arm 3 and Arm 4, the median time (95% CI) to achieve first MID response in ISS7 by Week 12 was 2.00 [2.00, 3.00] weeks for the mITT Set.
For the PP Set, similar result to that of the mITT Set was reported.

Table 27: Time to Minimally Important Difference by Week 12 in Weekly Itch Severity Score – (mITT Set)

	Arm 1 (N = 203)	Arm 2 (N = 205)	Arm 3 (N = 107)	Arm 4 (N = 103)
Number (%) of MID responders	173 (85.2%)	173 (84.4%)	88 (82.2%)	87 (84.5%)
Time to MID in ISS7 (in weeks)				
25th percentile [95% CI]	1.00 [NE, NE]	1.00 [1.00, 2.00]	1.00 [NE, NE]	1.00 [1.00, 2.00]
Median [95% CI]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]
75th percentile [95% CI]	6.00 [5.00, 8.00]	5.00 [5.00, 7.00]	6.00 [5.00, 12.00]	6.00 [5.00, 9.00]
Minimum, Maximum	1.0, 12.1	0.9, 12.1	0.7, 12.0	1.0, 12.0

Percentage of Minimally Important Difference Responders in Weekly Itch Severity Score at Weeks 8, 12, and 24

Treatment Period I

For the dose level of 300 mg, the numbers (percentages) of MID responders in ISS7 were 129 (63.5%) patients in Arm 1 and 149 (72.7%) patients in Arm 2 at Week 8, and 141 (69.5%) patients in Arm 1 and 152 (74.1%) patients in Arm 2 at Week 12 for the mITT Set.

For the dose level of 150 mg, the numbers (percentages) of MID responders in ISS7 were 70 (65.4%) patients in Arm 3 and 62 (60.2%) patients in Arm 4 at Week 8, and 78 (72.9%) patients in Arm 3 and 65 (63.1%) patients in Arm 4 at Week 12, respectively, for the mITT Set.
For the PP Set, similar result to that of the mITT Set was reported.

Table 28: Percentage of Minimally Important Difference Responders in Weekly Itch Severity Score – (mITT Set) – Treatment Period I

Study Week	Arm 1 (N = 203)	Arm 2 (N = 205)	Arm 3 (N = 107)	Arm 4 (N = 103)
	Number (%) of Patients			
Week 8				
Number of evaluable patients	190	195	101	95
MID responders	129 (63.5%)	149 (72.7%)	70 (65.4%)	62 (60.2%)
Week 12				
Number of evaluable patients	186	192	101	94
MID responders	141 (69.5%)	152 (74.1%)	78 (72.9%)	65 (63.1%)

Abbreviations: Arm 1 = CT-P39 300 mg; Arm 2 = Xolair 300 mg; Arm 3 = CT-P39 150 mg; Arm 4 = Xolair 150 mg; MID = Minimally important difference; mITT = Modified Intent-to-Treat; N = Total number of patients.

Note: The MID response in weekly itch severity score (ISS7) was defined as a reduction of 5 points or more from baseline for ISS7 at each timepoint. If a patient had missing weekly scores for the given week the patient was classified as a non-responder.

Treatment Period II

During Treatment Period II, the numbers (percentages) of MID responders in ISS7 at Week 24 were similar among Arm 1, Arm 2-1, and Arm 2-2 (145 [77.5%] patients in Arm 1, 78 [81.3%] patients in Arm 2-1, and 71 [74.0%] patients in Arm 2-2) for the mITT-TP2 Subset.

In Arm 3 and Arm 4, in which dose increased from 150 mg to 300 mg, the numbers (percentages) of MID responders in ISS7 at Week 24 were 76 (75.2%) patients and 72 (73.5%) patients, respectively, for the mITT-TP2 Subset.

Table 29: Percentage of Minimally Important Difference Responders in Weekly Itch Severity Score – (mITT-TP2 Subset) – Treatment Period II

Study Week	Arm 1 (N = 187)	Arm 2-1 (N = 96)	Arm 2-2 (N = 96)	Arm 3 (N = 101)	Arm 4 (N = 98)
	Number (%) of Patients				
Week 24					
Number of evaluable patients	169	88	82	90	86
MID responders	145 (77.5%)	78 (81.3%)	71 (74.0%)	76 (75.2%)	72 (73.5%)

Abbreviations: Arm 1 = CT-P39 300 mg Maintenance; Arm 2-1 = Switched from Xolair to CT-P39 300 mg after Week 12; Arm 2-2 = Xolair 300 mg Maintenance; Arm 3 = Dose increased from CT-P39 150 mg to 300 mg after Week 12; Arm 4 = Dose increased from Xolair 150 mg to 300 mg after Week 12; mITT = Modified Intent-to-Treat; N = Total number of patients; TP2 = Treatment Period II.

Note: The minimally important difference response in weekly itch severity score (ISS7) was defined as a reduction of 5 points or more from baseline for ISS7 at each timepoint. If a patient had missing weekly scores for the given week the patient was classified as a non-responder.

Change from Baseline in Weekly Urticaria Activity Score at Weeks 8, 12, and 24

Treatment Period I

The mean UAS7 gradually decreased from baseline in all treatment arms throughout Treatment Period I.

For the dose level of 300 mg, the mean (SD) changes from baseline in UAS7 were -17.31 (12.64) points in Arm 1 and -19.23 (12.88) points in Arm 2 at Week 8 and -19.27 (12.53) points in Arm 1 and

-20.54 (12.69) points in Arm 2 at Week 12 for the mITT Set. Although there were the slight fluctuations by timepoints, the mean (SD) changes from baseline in ISS7 were comparable between Arm 1 and Arm 2 during Treatment Period I.
For the dose level of 150 mg, the mean (SD) changes from baseline in UAS7 were -17.47 (12.19) points in Arm 3 and -15.88 (11.72) points in Arm 4 at Week 8 and -19.84 (12.02) points and -18.21 (13.06) points at Week 12 for the mITT Set.
For the PP Set, similar result to that of the mITT Set was reported.

Treatment Period II

During Treatment Period II, the mean (SD) changes from baseline in UAS7 at Week 24 were similar among Arm 1, Arm 2-1, and Arm 2-2 (-23.12 [12.32] points in Arm 1, -24.96 [11.79] points in Arm 2-1, and -23.55 [12.08] points in Arm 2-2) for the mITT-TP2 Subset, which indicated that the reduction in UAS7 after a single transition from Xolair to CT-P39 was not different from those of patients maintained on CT-P39 or Xolair.

In Arm 3 and Arm 4, in which dose increased from 150 mg to 300 mg, the mean (SD) changes from baseline in UAS7 at Week 24 were -24.50 (11.13) points and -22.44 (11.81) points, respectively, for the mITT-TP2 Subset.

Table 30: Descriptive Statistics for Actual Result and Change from Baseline at Weeks 8 and 12 in Weekly Urticaria Activity Score – (mITT Set) – Treatment Period I

Study Week / Statistics	Arm 1 (N = 203)		Arm 2 (N = 205)		Arm 3 (N = 107)		Arm 4 (N = 103)	
	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline
Baseline								
n	203	-	205	-	107	-	103	-
Mean	31.74	-	31.20	-	31.43	-	32.22	-
SD	7.11	-	7.49	-	6.95	-	6.99	-
Minimum	5.3	-	0.0	-	15.0	-	17.0	-
Median	32.00	-	32.00	-	32.50	-	33.00	-
Maximum	42.0	-	42.0	-	42.0	-	42.0	-
Week 4								
n	198	198	201	201	102	102	99	99
Mean	18.26	-13.34	16.54	-14.60	18.21	-13.34	20.72	-11.35
SD	12.76	12.28	11.85	12.63	13.04	12.45	12.20	11.63
Minimum	0.0	-42.0	0.0	-42.0	0.0	-39.5	0.0	-37.5
Median	18.00	-11.50	15.50	-12.60	18.29	-14.00	21.00	-11.50
Maximum	42.0	13.0	42.0	20.5	42.0	7.0	42.0	6.5
Week 8								
n	190	190	195	195	101	101	95	95
Mean	14.17	-17.31	12.12	-19.23	14.13	-17.47	16.55	-15.88
SD	11.99	12.64	11.31	12.88	11.65	12.19	11.69	11.72
Minimum	0.0	-42.0	0.0	-42.0	0.0	-42.0	0.0	-41.3
Median	14.00	-18.25	13.00	-19.50	14.00	-17.50	14.50	-17.00
Maximum	42.0	21.3	42.0	16.5	42.0	3.8	42.0	3.5

Study Week Statistics	Arm 1 (N = 203)		Arm 2 (N = 205)		Arm 3 (N = 107)		Arm 4 (N = 103)	
	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline
Week 12								
n	186	186	192	192	101	101	94	94
Mean	12.25	-19.27	10.72	-20.54	11.48	-19.84	14.20	-18.21
SD	11.72	12.53	10.99	12.69	10.68	12.02	12.72	13.06
Minimum	0.0	-42.0	0.0	-42.0	0.0	-42.0	0.0	-42.0
Median	12.25	-21.00	9.17	-21.75	12.00	-20.50	12.75	-19.75
Maximum	42.0	18.0	42.0	17.0	42.0	3.8	42.0	11.5

Abbreviations: Arm 1 = CT-P39 300 mg; Arm 2 = Xolair 300 mg; Arm 3 = CT-P39 150 mg; Arm 4 = Xolair 150 mg; mITT = Modified Intent-to-Treat; n = Number of patients; N = Total number of patients; SD = Standard deviation.

Table 31: Descriptive Statistics for Actual Result and Change from Baseline at Week 24 in Weekly Urticaria Activity Score – (mITT-TP2 Subset) – Treatment Period II

Study Week Statistics	Arm 1 (N = 187)		Arm 2-1 (N = 96)		Arm 2-2 (N = 96)		Arm 3 (N = 101)		Arm 4 (N = 98)	
	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline
Baseline										
n	187	-	96	-	96	-	101	-	98	-
Mean	31.35	-	31.04	-	31.70	-	31.48	-	32.46	-
SD	7.14	-	7.29	-	7.06	-	6.92	-	6.86	-
Minimum	5.3	-	13.0	-	16.0	-	15.0	-	17.0	-
Median	32.00	-	31.00	-	32.00	-	32.50	-	33.25	-
Maximum	42.0	-	42.0	-	42.0	-	42.0	-	42.0	-
Week 24										
n	169	169	88	88	82	82	90	90	86	86
Mean	8.16	-23.12	5.79	-24.96	8.22	-23.55	7.48	-24.50	9.43	-22.44
SD	11.01	12.32	9.67	11.79	10.21	12.08	10.49	11.13	10.23	11.81
Minimum	0.0	-42.0	0.0	-42.0	0.0	-42.0	0.0	-42.0	0.0	-42.0
Median	1.50	-26.00	0.00	-27.00	3.75	-24.75	2.00	-28.00	7.00	-23.00
Maximum	42.0	14.5	42.0	13.5	42.0	13.5	42.0	4.0	42.0	4.0

Abbreviations: Arm 1 = CT-P39 300 mg Maintenance; Arm 2-1 = Switched from Xolair to CT-P39 300 mg after Week 12; Arm 2-2 = Xolair 300 mg Maintenance; Arm 3 = Dose increased from CT-P39 150 mg to 300 mg after Week 12; Arm 4 = Dose increased from Xolair 150 mg to 300 mg after Week 12; mITT = Modified Intent-to-Treat; n = Number of patients; N = Total number of patients; SD = Standard deviation; TP2 = Treatment Period II.

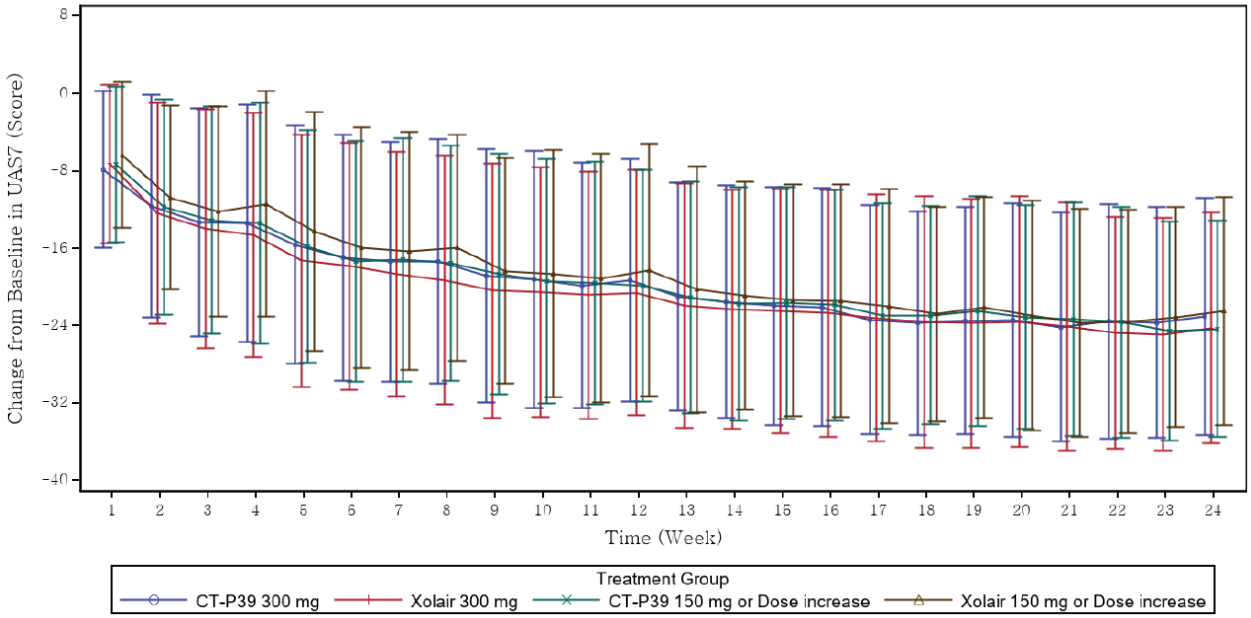


Figure 8. Mean (± SD) Plot of Change from Baseline in UAS7 mITT Set

Percentage of Patients with Weekly Urticaria Activity Score of ≤ 6 points and Complete Responders in Weekly Urticaria Activity Score at Weeks 8, 12, and 24

Treatment Period I

For the dose level of 300 mg, the numbers (percentages) of patients with UAS7 of ≤ 6 points at Week 8 were slightly lower in Arm 1 compared with Arm 2 (61 [30.0%] patients in Arm 1 and 81 [39.5%] patients in Arm 2), however, the numbers (percentages) of patients of complete responders in UAS7 at Week 8 were similar between Arm 1 and Arm 2 (40 [19.7%] patients in Arm 1 and 50 [24.4%] patients in Arm 2) for the mITT Set. The numbers (percentages) of patients with UAS7 of ≤ 6 points at Week 12 were similar between Arm 1 and Arm 2 (77 [37.9%] patients in Arm 1 and 83 [40.5%] patients in Arm 2), although the numbers (percentages) of complete responders in UAS7 at Week 12 were slightly lower in Arm 1 compared with Arm 2 (48 [23.6%] patients in Arm 1 and 63 [30.7%] patients in Arm 2) for the mITT Set. When considering the results of the percentages of patients with UAS7 of ≤ 6 points and complete responders together, no notable differences were found.

For the dose level of 150 mg, the numbers (percentages) of patients with UAS7 of ≤ 6 points at Week 8 were 35 (32.7%) patients in Arm 3 and 21 (20.4%) patients in Arm 4 and numbers (percentages) of complete responders in UAS7 at Week 8 were 21 (19.6%) patients in Arm 3 and 11 (10.7%) patients in Arm 4 for the mITT Set. The numbers (percentages) of patients with UAS7 of ≤ 6 points at Week 12 were 41 (38.3%) patients in Arm 3 and 33 (32.0%) patients in Arm 4 and the numbers (percentages) of complete responders in UAS7 at Week 12 were 23 (21.5%) patients in Arm 3 and 14 (13.6%) patients in Arm 4 for the mITT Set.
For the PP Set, similar result to that of the mITT Set was reported.

Table 32: Percentage of Patients with UAS7 of ≤ 6 points and Complete Responders in Weekly Urticaria Activity Score – (mITT Set) – Treatment Period I

Study Week	Arm 1 (N = 203)	Arm 2 (N = 205)	Arm 3 (N = 107)	Arm 4 (N = 103)
	Number (%) of Patients			
Week 8				
Number of evaluable patients	190	195	101	95
Patients with UAS7 ≤ 6	61 (30.0%)	81 (39.5%)	35 (32.7%)	21 (20.4%)
Patients with UAS7 = 0 (Complete responders)	40 (19.7%)	50 (24.4%)	21 (19.6%)	11 (10.7%)
Week 12				
Number of evaluable patients	186	192	101	94
Patients with UAS7 ≤ 6	77 (37.9%)	83 (40.5%)	41 (38.3%)	33 (32.0%)
Patients with UAS7 = 0 (Complete responders)	48 (23.6%)	63 (30.7%)	23 (21.5%)	14 (13.6%)

Abbreviation: Arm 1 = CT-P39 300 mg; Arm 2 = Xolair 300 mg; Arm 3 = CT-P39 150 mg; Arm 4 = Xolair 150 mg; mITT = Modified Intent-to-Treat; N = Total number of patients; UAS7 = Weekly Urticaria Activity Score.

Note: If a patient had missing weekly scores for the given week the patient was classified as a non-responder.

Treatment Period II

During Treatment Period II, the numbers (percentages) of patients with UAS7 of ≤ 6 points and complete responders in UAS7 at Week 24 were slightly higher in Arm 2-1 than those of Arm 1 and Arm 2-2 (102 [54.5%] patients and 75 [40.1%] patients in Arm 1, 65 [67.7%] patients and 49 [51.0%] patients in Arm 2-1, and 46 [47.9%] patients and 36 [37.5%] patients in Arm 2-2) for the mITT-TP2 Subset, which indicated that transition from Xolair to CT-P39 did not negatively affect the efficacy response compared to maintenance on CT-P39 or Xolair in terms of controlling UAS7 to ≤ 6 points and the complete response in UAS7.

In Arm 3 and Arm 4, in which dose increased from 150 mg to 300 mg, the numbers (percentages) of patients with UAS7 of ≤ 6 points at Week 24 were 55 (54.5%) patients and 41 (41.8%) patients and the numbers (percentages) of complete responders in UAS7 at Week 24 were 39 (38.6%) patients and 31 (31.6%) patients, respectively, for the mITT-TP2 Subset.

Table 33: Percentage of Patients with UAS7 of ≤ 6 points and Complete Responders in Weekly Urticaria Activity Score – (mITT-TP2 Set) – Treatment Period

Study Week	Arm 1 (N = 187)	Arm 2-1 (N = 96)	Arm 2-2 (N = 96)	Arm 3 (N = 101)	Arm 4 (N = 98)
	Number (%) of Patients				
Week 24					
Number of evaluable patients	169	88	82	90	86
Patients with UAS7 of ≤ 6	102 (54.5%)	65 (67.7%)	46 (47.9%)	55 (54.5%)	41 (41.8%)
Patients with UAS7 = 0 (Complete responders)	75 (40.1%)	49 (51.0%)	36 (37.5%)	39 (38.6%)	31 (31.6%)

Abbreviation: Arm 1 = CT-P39 300 mg Maintenance; Arm 2-1 = Switched from Xolair to CT-P39 300 mg after Week 12; Arm 2-2 = Xolair 300 mg Maintenance; Arm 3 = Dose increased from CT-P39 150 mg to 300 mg after Week 12; Arm 4 = Dose increased from Xolair 150 mg to 300 mg after Week 12; mITT = Modified Intent-to-Treat; N = Total number of patients; TP2 = Treatment Period II; UAS7 = Weekly Urticaria Activity Score.

Note: If a patient had missing weekly scores for the given week the patient was classified as a non-responder.

Change from Baseline in the Weekly Hives Severity Score at Weeks 8, 12, and 24

Treatment Period I

The mean HSS7 gradually decreased from baseline in all treatment arms throughout Treatment Period I.
For the dose level of 300 mg, the mean (SD) changes from baseline in HSS7 were -8.99 (6.84) points in Arm 1 and -10.02 (7.02) points in Arm 2 at Week 8 and -9.96 (6.88) points in Arm 1 and -10.55 (6.93) points in Arm 2 at Week 12 for the mITT Set. Although there were the slight fluctuations by timepoints, the mean (SD) changes from baseline in HSS7 were comparable between Arm 1 and Arm 2 during Treatment Period I.
For the dose level of 150 mg, the mean changes from baseline in HSS7 were -9.15 (6.60) points in Arm 3 and -8.25 (6.41) points in Arm 4 at Week 8 and -10.29 (6.75) points in Arm 3 and -9.48 (6.93) points in Arm 4 at Week 12 for the mITT Set.

For the PP Set, similar result to that of the mITT Set was reported.

Treatment Period II

During Treatment Period II, the mean (SD) changes from baseline in HSS7 at Week 24 were similar among Arm 1, Arm 2-1, and Arm 2-2 (-11.88 [6.73] points in Arm 1, -12.72 [6.72] points in Arm 2-1, and -12.36 [6.64] points in Arm 2-2) for the mITT-TP2 Subset, which indicated that the reduction in HSS7 after a single transition from Xolair to CT-P39 was not different from those of patients maintained on CT-P39 or Xolair.
In Arm 3 and Arm 4, in which dose increased from 150 mg to 300 mg, the mean (SD) changes from baseline in HSS7 at Week 24 were -12.74 (6.01) points and -11.76 (6.19) points, respectively, for the mITT-TP2 Subset.

Table 34: Descriptive Statistics for Actual Result and Change from Baseline at Weeks 8 and 12 in Weekly Hives Severity Score – (mITT Set) – Treatment Period I

Study Week	Arm 1 (N = 203)		Arm 2 (N = 205)		Arm 3 (N = 107)		Arm 4 (N = 103)	
Statistics	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline
Baseline								
n	203	-	205	-	107	-	103	-
Mean	16.07	-	15.93	-	15.91	-	16.47	-
SD	4.56	-	4.50	-	4.55	-	4.39	-
Minimum	2.5	-	0.0	-	0.0	-	6.0	-
Median	16.50	-	16.00	-	16.50	-	17.00	-
Maximum	21.0	-	21.0	-	21.0	-	21.0	-
Week 4								
n	198	198	201	201	102	102	99	99
Mean	9.15	-6.87	8.27	-7.65	9.24	-6.70	10.63	-5.71
SD	6.98	6.70	6.53	7.00	7.06	6.71	6.90	6.27
Minimum	0.0	-21.0	0.0	-21.0	0.0	-21.0	0.0	-21.0
Median	7.50	-6.50	7.00	-6.50	8.45	-6.79	9.50	-5.17
Maximum	21.0	8.5	21.0	9.4	21.0	5.5	21.0	4.5
Week 8								
n	190	190	195	195	101	101	95	95
Mean	6.98	-8.99	5.96	-10.02	6.87	-9.15	8.40	-8.25
SD	6.41	6.84	6.01	7.02	6.23	6.60	6.60	6.41
Minimum	0.0	-21.0	0.0	-21.0	0.0	-21.0	0.0	-21.0
Median	7.00	-10.00	6.00	-10.50	7.00	-8.50	7.00	-7.88
Maximum	21.0	11.5	21.0	9.5	21.0	3.0	21.0	3.5

Study Week Statistics	Arm 1 (N = 203)		Arm 2 (N = 205)		Arm 3 (N = 107)		Arm 4 (N = 103)	
	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline
Week 12								
n	186	186	192	192	101	101	94	94
Mean	6.07	-9.96	5.39	-10.55	5.61	-10.29	7.12	-9.48
SD	6.21	6.88	5.87	6.93	5.90	6.75	7.09	6.93
Minimum	0.0	-21.0	0.0	-21.0	0.0	-21.0	0.0	-21.0
Median	6.00	-10.75	4.50	-11.50	5.00	-12.08	6.00	-10.00
Maximum	21.0	13.5	21.0	9.0	21.0	5.4	21.0	6.0

Abbreviations: Arm 1 = CT-P39 300 mg; Arm 2 = Xolair 300 mg, Arm 3 = CT-P39 150 mg; Arm 4 = Xolair 150 mg; mITT = Modified Intent-to-Treat; n = Number of patients; N = Total number of patients; SD = Standard deviation.

Table 35: Descriptive Statistics for Actual Result and Change from Baseline at Week 24 in Weekly Hives Severity Score –(mITT-TP2 Subset) – Treatment Period II

Study Week Statistics	Arm 1 (N = 187)		Arm 2-1 (N = 96)		Arm 2-2 (N = 96)		Arm 3 (N = 101)		Arm 4 (N = 98)	
	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline	Actual Result (points)	Change from Baseline
Baseline										
n	187	-	96	-	96	-	101	-	98	-
Mean	15.91	-	15.73	-	16.34	-	16.04	-	16.69	-
SD	4.59	-	4.40	-	4.32	-	4.36	-	4.27	-
Minimum	2.5	-	2.0	-	7.0	-	0.0	-	6.0	-
Median	16.50	-	15.75	-	16.50	-	16.50	-	17.25	-
Maximum	21.0	-	21.0	-	21.0	-	21.0	-	21.0	-
Week 24										
n	169	169	88	88	82	82	90	90	86	86
Mean	4.03	-11.88	2.88	-12.72	3.99	-12.36	3.59	-12.74	4.51	-11.76
SD	5.85	6.73	5.22	6.72	5.25	6.64	5.56	6.01	5.22	6.19
Minimum	0.0	-21.0	0.0	-21.0	0.0	-21.0	0.0	-21.0	0.0	-21.0
Median	0.00	-13.50	0.00	-14.00	0.83	-12.79	0.25	-14.00	1.50	-12.75
Maximum	21.0	9.5	21.0	10.0	21.0	6.0	21.0	2.0	21.0	0.0

Abbreviations: Arm 1 = CT-P39 300 mg Maintenance; Arm 2-1 = Switched from Xolair to CT-P39 300 mg after Week 12; Arm 2-2 = Xolair 300 mg Maintenance; Arm 3 = Dose increased from CT-P39 150 mg to 300 mg after Week 12; Arm 4 = Dose increased from Xolair 150 mg to 300 mg after Week 12; mITT = Modified Intent-to-Treat; n = Number of patients; N = Total number of patients; SD = Standard deviation; TP2 = Treatment Period II.

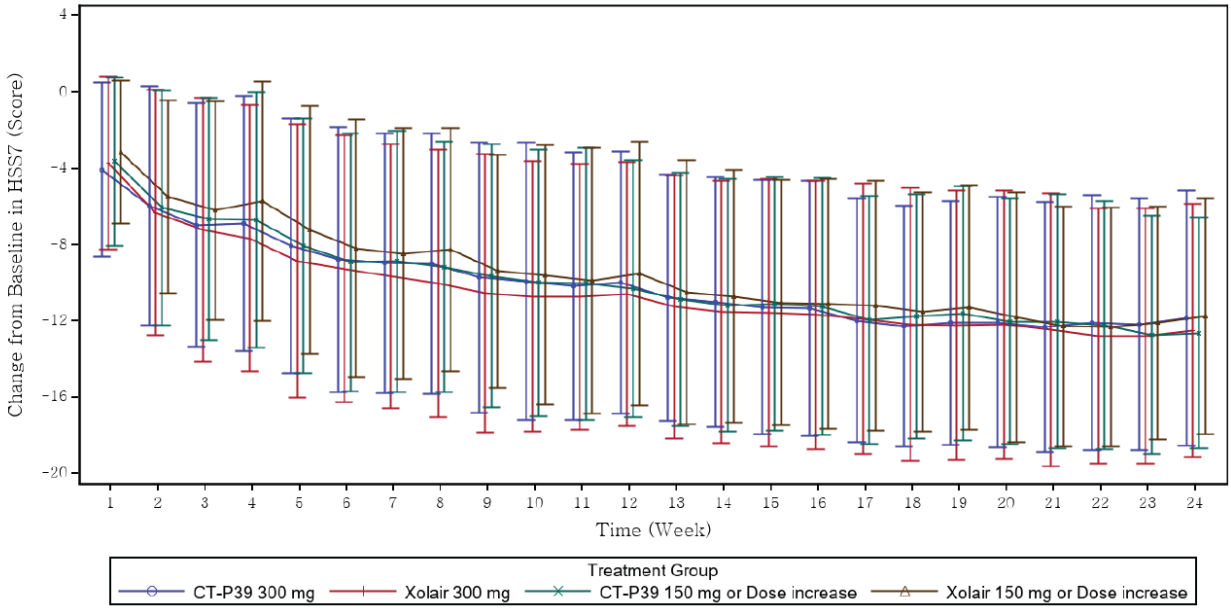


Figure 9. Mean (± SD) Plot of Change from Baseline in HSS7 mITT Set

Additional post-hoc analyses were provided by the applicant in response to questions:

Table 36: Statistical Analysis of Mean Change from Baseline in Weekly Symptom Severity Scores at Weeks 6, 8, 10, and 12 (ANCOVA) in Study CT-P39 3.1: mITT Set

	CT-P39 300 mg (N=203)	Xolair 300 mg (N=205)
Mean Change from Baseline in ISS7 at Week 6		
n	194	196
LS Mean (SE)	-7.58 (0.822)	-8.06 (0.827)
Estimate of Treatment Difference (95% CI)	0.48 (-0.68, 1.64)	
Mean Change from Baseline in ISS7 at Week 8		
n	190	195
LS Mean (SE)	-7.89 (0.811)	-8.81 (0.815)
Estimate of Treatment Difference (95% CI)	0.92 (-0.23, 2.07)	
Mean Change from Baseline in ISS7 at Week 10		
n	187	195
LS Mean (SE)	-9.52 (0.859)	-10.10 (0.857)
Estimate of Treatment Difference (95% CI)	0.58 (-0.57, 1.73)	
Mean Change from Baseline in ISS7 at Week 12		
n	186	192
LS Mean (SE)	-9.21 (0.796)	-9.98 (0.798)
Estimate of Treatment Difference (95% CI)	0.77 (-0.37, 1.90)	
Mean Change from Baseline in HSS7 at Week 6		
n	194	196
LS Mean (SE)	-7.81 (0.881)	-8.32 (0.886)
Estimate of Treatment Difference (95% CI)	0.51 (-0.74, 1.75)	
Mean Change from Baseline in HSS7 at Week 8		
n	190	195
LS Mean (SE)	-8.24 (0.854)	-9.21 (0.859)

	CT-P39 300 mg (N=203)	Xolair 300 mg (N=205)
Estimate of Treatment Difference (95% CI)	0.97 (-0.24, 2.18)	
Mean Change from Baseline in HSS7 at Week 10		
n	187	195
LS Mean (SE)	-9.79 (0.910)	-10.45 (0.908)
Estimate of Treatment Difference (95% CI)	0.66 (-0.56, 1.88)	
Mean Change from Baseline in HSS7 at Week 12		
n	186	192
LS Mean (SE)	-9.25 (0.844)	-9.89 (0.847)
Estimate of Treatment Difference (95% CI)	0.64 (-0.56, 1.85)	
Mean Change from Baseline in UAS7 at Week 6		
n	194	196
LS Mean (SE)	-15.36 (1.651)	-16.37 (1.660)
Estimate of Treatment Difference (95% CI)	1.01 (-1.32, 3.33)	
Mean Change from Baseline in UAS7 at Week 8		
n	190	195
LS Mean (SE)	-16.11 (1.617)	-18.00 (1.625)
Estimate of Treatment Difference (95% CI)	1.90 (-0.39, 4.19)	
Mean Change from Baseline in UAS7 at Week 10		
n	187	195
LS Mean (SE)	-19.33 (1.722)	-20.58 (1.717)
Estimate of Treatment Difference (95% CI)	1.25 (-1.06, 3.55)	
Mean Change from Baseline in UAS7 at Week 12		
n	186	192
LS Mean (SE)	-18.43 (1.597)	-19.86 (1.601)
Estimate of Treatment Difference (95% CI)	1.43 (-0.85, 3.70)	

Abbreviations: CI, Confidence interval; HSS7, Weekly hives severity score; ISS7, Weekly itch severity score; LS, Least squares; mITT, Modified intent-to-treat; N, Total number of patients; n, Number of patients; SE, Standard error; UAS7, Weekly urticaria activity score

Note: An ANCOVA is performed with the treatment as a fixed effect and baseline weekly scores, body weight on Day 1 and country as covariates.

Table 37: Statistical Test for Proportion of Patients Achieving Response at Weeks 6, 8, 10 and 12 in Study CT-P39 3.1: mITT Set

	CT-P39 300 mg (N = 203)	Xolair 300 mg (N = 205)
Percentage of MID Responders in ISS7 at Week 6		
n (%)	131 (64.5%)	136 (66.3%)
Estimate of Treatment Difference (95% CI)	-1.81 (-11.04, 7.42)	
Percentage of MID Responders in ISS7 at Week 8		
n (%)	129 (63.5%)	149 (72.7%)
Estimate of Treatment Difference (95% CI)	-9.14 (-18.14, -0.13)	
Percentage of MID Responders in ISS7 at Week 10		
n (%)	140 (69.0%)	156 (76.1%)
Estimate of Treatment Difference (95% CI)	-7.13 (-15.77, 1.50)	
Percentage of MID Responders in ISS7 at Week 12		
n (%)	141 (69.5%)	152 (74.1%)
Estimate of Treatment Difference (95% CI)	-4.69 (-13.41, 4.03)	

	CT-P39 300 mg (N = 203)	Xolair 300 mg (N = 205)
Percentage of Patient with UAS of ≤6 at Week 6		
n (%)	64 (31.5%)	70 (34.1%)
Estimate of Treatment Difference (95% CI)	-2.62 (-11.73, 6.49)	
Percentage of Patient with UAS of ≤6 at Week 8		
n (%)	61 (30.0%)	81 (39.5%)
Estimate of Treatment Difference (95% CI)	-9.46 (-18.66, -0.27)	
Percentage of Patient with UAS of ≤6 at Week 10		
n (%)	79 (38.9%)	87 (42.4%)
Estimate of Treatment Difference (95% CI)	-3.52 (-13.05, 6.00)	
Percentage of Patient with UAS of ≤ 6 at Week 12		
n (%)	77 (37.9%)	83 (40.5%)
Estimate of Treatment Difference (95% CI)	-2.56 (-12.03, 6.91)	
Percentage of Complete Responders (UAS = 0) at Week 6		
n (%)	32 (15.8%)	39 (19.0%)
Estimate of Treatment Difference (95% CI)	-3.26 (-10.61, 4.09)	
Percentage of Complete Responders (UAS = 0) at Week 8		
n (%)	40 (19.7%)	50 (24.4%)
Estimate of Treatment Difference (95% CI)	-4.69 (-12.72, 3.35)	
Percentage of Complete Responders (UAS = 0) at Week 10		
n (%)	49 (24.1%)	55 (26.8%)
Estimate of Treatment Difference (95% CI)	-2.69 (-11.14, 5.76)	
Percentage of Complete Responders (UAS = 0) at Week 12		
n (%)	48 (23.6%)	63 (30.7%)
Estimate of Treatment Difference (95% CI)	-7.09 (-15.69, 1.52)	

Abbreviations: CI, Confidence interval; ISS7, Weekly itch severity score; MID, Minimal important difference; mITT, Modified intent-to-treat; N, Total number of patients; n, Number of patients; UAS7, Weekly urticaria activity score
Note: The difference on proportion and its 95% confidence interval (CI) of two treatment group is produced using Wald method.

Table 38: Statistical Analysis of Responder Rate Between the 2 Dose Levels in Each Treatment at Week 8 and Week 12 (mITT Set)

	CT-P39		Xolair	
	CT-P39 300 mg (N = 203)	CT-P39 150 mg (N = 107)	Xolair 300 mg (N = 205)	Xolair 150 mg (N = 103)
Percentage of MID responders in ISS7 at Week 8				
Response rate (n [%])	129 (63.5%)	70 (65.4%)	149 (72.7%)	62 (60.2%)
Difference (95% CI)	-1.87 (-13.06, 9.31)		12.49 (1.24, 23.74)	
Percentage of MID responders in ISS7 at Week 12				
Response rate (n [%])	141 (69.5%)	78 (72.9%)	152 (74.1%)	65 (63.1%)
Difference (95% CI)	-3.44 (-13.98, 7.10)		11.04 (-0.04, 22.12)	
Percentage of Patient with UAS of ≤6 at Week 8				
Response rate (n [%])	61 (30.0%)	35 (32.7%)	81 (39.5%)	21 (20.4%)
Difference (95% CI)	-2.66 (-13.56, 8.24)		19.12 (8.86, 29.39)	
Percentage of Patient with UAS of ≤6 at Week 12				
Response rate (n [%])	77 (37.9%)	41 (38.3%)	83 (40.5%)	33 (32.0%)
Difference (95% CI)	-0.39 (-11.76, 10.99)		8.45 (-2.79, 19.69)	

	CT-P39		Xolair	
	CT-P39 300 mg (N = 203)	CT-P39 150 mg (N = 107)	Xolair 300 mg (N = 205)	Xolair 150 mg (N = 103)
Percentage of Patient with UAS = 0 at Week 8				
Response rate (n [%])	40 (19.7%)	21 (19.6%)	50 (24.4%)	11 (10.7%)
Difference (95% CI)	0.08 (-9.23, 9.38)		13.71 (5.34, 22.09)	
Percentage of Patient with UAS = 0 at Week 12				
Response rate (n [%])	48 (23.6%)	23 (21.5%)	63 (30.7%)	14 (13.6%)
Difference (95% CI)	2.15 (-7.58, 11.88)		17.14 (7.99, 26.29)	

Abbreviations: CI, Confidence interval; ISS7, Weekly itch severity score; mITT, modified Intent-To-Treat; MID, Minimal important difference; N, Total number of patients; n, Number of patients; UAS7, Weekly urticaria activity score

Note: The difference on proportion and its 95% confidence interval (CI) of two treatment group is produced using Wald method.

Percentage of Angioedema-Free Days from Week 4 to Week 12

The mean percentages of angioedema-free days from Week 4 to Week 12 were similar between 300 mg treatment arms (93.47% in Arm 1 and 90.14% in Arm 2) for the mITT Set.
In Arm 3 and Arm 4, the mean percentages of angioedema-free days from Week 4 to Week 12 were 96.94% and 93.77% for the mITT Set, respectively.
For the PP Set, similar result to that of the mITT Set was reported.

Table 39: Descriptive Statistics for Percentage of Angioedema-Free Days – (mITT Set) Statistic

Statistic	Arm 1 (N = 203)	Arm 2 (N = 205)	Arm 3 (N = 107)	Arm 4 (N = 103)
Percentage of Angioedema-Free Days from Week 4 to Week 12 (%)				
n	189	190	99	97
Mean	93.47	90.14	96.94	93.77
SD	17.95	25.64	10.83	18.01
Minimum	0.0	0.0	24.5	0.0
Median	100.00	100.00	100.00	100.00
Maximum	100.0	100.0	100.0	100.0

Abbreviations: Arm 1 = CT-P39 300 mg; Arm 2 = Xolair 300 mg; Arm 3 = CT-P39 150 mg; Arm 4 = Xolair 150 mg; eDiary = Electronic diary; mITT = Modified Intent-to-Treat; n = Number of patients; N = Total number of patients; SD = Standard deviation.

Note: Angioedema-free days was defined as the number of days for which the patients indicated a 'No' response to the angioedema question in the patient eDiary. The proportion was based on data collected in the patient eDiary from Week 4 to Week 12 defined as the number of angioedema-free days divided by the total number of days with a non–missing diary entry starting on Week 4 date and ending the day prior to Week 12 date. Patients who had missing responses for > 40% of the daily diary entries between Week 4 and Week 12 were not included in this analysis.

Change from Baseline in Number of Tablets/Week of Rescue Therapy at Weeks 8, 12, and 24

Treatment Period I

The mean number of tablets/week of rescue therapy decreased from baseline in all treatment arms throughout Treatment Period I.

The mean (SD) changes from baseline in mean number of tablets/week of rescue therapy were similar between 300 mg treatment arms at Week 8 (-1.40 [2.66] in Arm 1 and -1.45 [3.39] in Arm 2) and at Week 12 (-1.37 [3.78] in Arm 1 and -1.49 [3.19] in Arm 2), for the mITT Set. In Arm 3 and Arm 4, the mean (SD) changes from baseline in mean number of tablets/week of rescue therapy were -1.00 (2.59) and -1.09 (3.10) at Week 8 and -1.21 (2.73) and -1.53 (3.42) at Week 12, respectively, for the mITT Set.
For the PP Set, similar result to that of the mITT Set was reported.

Treatment Period II

During Treatment Period II, the mean (SD) changes from baseline in number of tablets/week of rescue therapy at Week 24 were similar among Arm 1, Arm 2-1, and Arm 2-2 (-1.46 [3.85] in Arm 1, -1.80 [3.71] in Arm 2-1, and -1.79 [3.01] in Arm 2-2) for the mITT-TP2 Subset.

In Arm 3 and Arm 4, in which dose increased from 150 mg to 300 mg, the mean (SD) changes from baseline in number of tablets/week of rescue therapy at Week 24 were -1.54 (3.39) and -1.77 (3.33), respectively, for the mITT-TP2 Subset.

Table 40: Descriptive Statistics for Actual Result and Change from Baseline in Number of Tablets/Week of Rescue Therapy at Weeks 8 and 12 – (mITT Set) – Treatment Period I

Study Week	Arm 1 (N = 203)		Arm 2 (N = 205)		Arm 3 (N = 107)		Arm 4 (N = 103)	
Statistics	Actual Result (Tablets)	Change from Baseline	Actual Result (Tablets)	Change from Baseline	Actual Result (Tablets)	Change from Baseline	Actual Result (Tablets)	Change from Baseline
Baseline								
n	180	-	188	-	99	-	95	-
Mean	3.49	-	3.73	-	3.24	-	3.61	-
SD	3.06	-	3.65	-	3.19	-	3.90	-
Minimum	0.0	-	0.0	-	0.0	-	0.0	-
Median	3.50	-	3.00	-	2.00	-	2.00	-
Maximum	7.0	-	28.0	-	7.0	-	24.0	-
Week 8								
n	166	165	180	180	93	93	88	88
Mean	2.08	-1.40	2.29	-1.45	2.21	-1.00	2.42	-1.09
SD	2.91	2.66	3.13	3.39	3.19	2.59	3.16	3.10
Minimum	0.0	-7.0	0.0	-21.0	0.0	-7.0	0.0	-17.0
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Maximum	7.0	7.0	7.0	7.0	11.0	10.0	7.0	7.0
Week 12								
n	166	165	176	176	90	90	86	85
Mean	2.04	-1.37	2.06	-1.49	1.90	-1.21	1.85	-1.53
SD	3.60	3.78	3.01	3.19	2.99	2.73	2.92	3.42
Minimum	0.0	-7.0	0.0	-7.0	0.0	-7.0	0.0	-17.0
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Maximum	29.8	29.8	7.0	7.0	7.0	7.0	8.0	7.0

Abbreviations: Arm 1 = CT-P39 300 mg; Arm 2 = Xolair 300 mg; Arm 3 = CT-P39 150 mg; Arm 4 = Xolair 150 mg; mITT = Modified Intent-To-Treat; n = Number of patients; N = Total number of patients; SD = Standard deviation.

Table 41: Descriptive Statistics for Actual Result and Change from Baseline in Number of Tablets/Week of Rescue Therapy at Week 24 – (mITT-TP2 Subset) – Treatment Period II

Study Week / Statistics	Arm 1 (N = 187)		Arm 2-1 (N = 96)		Arm 2-2 (N = 96)		Arm 3 (N = 101)		Arm 4 (N = 98)	
	Actual Result (Tablets)	Change from Baseline	Actual Result (Tablets)	Change from Baseline	Actual Result (Tablets)	Change from Baseline	Actual Result (Tablets)	Change from Baseline	Actual Result (Tablets)	Change from Baseline
Baseline										
n	166	-	84	-	92	-	93	-	90	-
Mean	3.53	-	3.38	-	3.72	-	3.17	-	3.53	-
SD	3.02	-	3.22	-	3.16	-	3.20	-	3.85	-
Minimum	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-
Median	4.00	-	3.00	-	4.00	-	2.00	-	2.00	-
Maximum	7.0	-	7.0	-	7.0	-	7.0	-	24.0	-
Week 24										
n	149	148	76	76	77	77	79	79	79	78
Mean	1.95	-1.46	1.61	-1.80	1.73	-1.79	1.60	-1.54	1.72	-1.77
SD	3.73	3.85	2.82	3.71	2.69	3.01	3.63	3.39	2.93	3.33
Minimum	0.0	-7.0	0.0	-7.0	0.0	-7.0	0.0	-7.0	0.0	-17.0
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Maximum	28.0	21.0	8.0	8.0	7.0	3.0	24.0	17.0	7.0	7.0

Abbreviations: Arm 1 = CT-P39 300 mg Maintenance; Arm 2-1 = Switched from Xolair to CT-P39 300 mg after Week 12; Arm 2-2 = Xolair 300 mg Maintenance; Arm 3 = Dose increased from CT-P39 150 mg to 300 mg after Week 12; Arm 4 = Dose increased from Xolair 150 mg to 300 mg after Week 12; mITT = Modified Intent-to-Treat; n = Number of patients; N = Total number of patients; SD = Standard deviation; TP2 = Treatment Period II.

Note: The number of tablets of rescue therapy was defined as the sum of daily use of rescue therapy over the study days which made up a given study week. The maximum permitted number of tablets per day were considered as 1, regardless of selected rescue medication. The patients who started a different medication or whose prescribed dose of the rescue therapy medication was changed during the study are excluded from the analysis.

- **Ancillary analyses**

The change from baseline at Week 12 in ISS7 analysis was also examined in the demographic subgroup and disease factor subgroup. There are some discrepancies in difference of change in ISS7 at Week 12 for each subgroup in the age, race, and country in demographic subgroup analyses and in duration of disease prior to baseline and previous number of CSU medications in disease factor subgroup analyses. The discrepancies were due to the small number of patients and are not powered subgroup analyses. Therefore, it is hard to draw a conclusion from the subgroup analyses.

Subgroup	CT-P39 300mg n	CT-P39 300mg LS Mean (SE)	Xolair 300mg n	Xolair 300mg LS Mean (SE)	Mean Difference (95% CI)
All Patients	186	-9.21 (0.796)	192	-9.98 (0.798)	0.77 (-0.37, 1.90)
Gender					
Female	123	-9.15 (1.092)	123	-9.95 (1.047)	0.80 (-0.66, 2.26)
Male	63	-8.49 (1.181)	69	-9.09 (1.271)	0.59 (-1.22, 2.41)
Age					
12-17 years	2	-8.11 (NA)	3	-6.32 (NA)	-1.79 (NA, NA)
18-64 years	173	-9.11 (0.815)	179	-10.05 (0.818)	0.94 (-0.26, 2.14)
>=65 years	11	-11.02 (1.991)	10	-10.88 (1.777)	-0.14 (-4.51, 4.24)
Race					
Asian	35	-9.18 (0.936)	38	-11.94 (0.898)	2.76 (0.17, 5.35)
White	151	-9.23 (0.937)	154	-9.52 (0.941)	0.29 (-0.97, 1.56)
Country [1]					
Bulgaria	38	-8.58 (0.780)	40	-8.27 (0.760)	-0.31 (-2.48, 1.87)
Korea	35	-9.18 (0.936)	38	-11.94 (0.898)	2.76 (0.17, 5.35)
Poland	81	-9.55 (0.608)	81	-10.20 (0.608)	0.64 (-1.06, 2.35)
Ukraine	28	-9.76 (1.304)	30	-9.25 (1.260)	-0.51 (-4.15, 3.13)
Body Weight at Day1					
<80 kg	111	-9.63 (1.201)	116	-10.20 (1.167)	0.57 (-0.92, 2.06)
>=80 kg	75	-9.21 (1.243)	76	-9.98 (1.289)	0.77 (-1.00, 2.55)

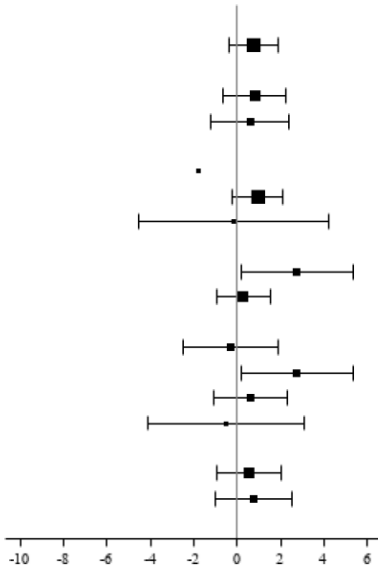


Figure 10. Forest Plot of Change from Baseline at Week 12 in ISS7 by Demographic Subgroup (mITT Set)

Subgroup	CT-P39 300mg n	CT-P39 300mg LS Mean (SE)	Xolair 300mg n	Xolair 300mg LS Mean (SE)	Mean Difference (95% CI)
All Patients	186	-9.21 (0.796)	192	-9.98 (0.798)	0.77 (-0.37, 1.90)
Baseline ISS7					
<13 points	34	-5.63 (1.224)	39	-5.77 (1.288)	0.14 (-2.11, 2.40)
>=13 points	152	-10.08 (0.893)	153	-11.00 (0.892)	0.92 (-0.40, 2.23)
Baseline UAS7					
<Median	90	-7.44 (0.767)	95	-7.51 (0.785)	0.07 (-1.42, 1.56)
>=Median	96	-9.99 (1.272)	97	-11.23 (1.304)	1.24 (-0.50, 2.97)
Baseline total IgE					
<Median	90	-9.41 (0.999)	95	-10.29 (0.994)	0.88 (-0.77, 2.53)
>=Median	93	-8.49 (1.430)	96	-8.75 (1.434)	0.26 (-1.38, 1.90)
Presence of angioedema at baseline					
Yes	61	-10.76 (1.412)	66	-9.85 (1.277)	-0.90 (-2.95, 1.14)
No	121	-8.55 (0.750)	122	-9.85 (0.804)	1.30 (-0.08, 2.68)
Duration of disease prior to baseline [1]					
<=1 year	54	-9.16 (0.949)	71	-11.28 (0.899)	2.12 (0.24, 4.00)
2-10 years	117	-7.67 (1.252)	110	-7.72 (1.297)	0.05 (-1.47, 1.57)
>10 years	15	-7.31 (2.530)	11	-7.20 (2.911)	-0.11 (-5.32, 5.09)
Previous number of CSU medications [2]					
<=2	86	-8.24 (0.867)	75	-8.54 (0.936)	0.30 (-1.48, 2.09)
3-5	64	-9.51 (1.149)	88	-10.11 (1.142)	0.60 (-1.10, 2.29)
>5	36	-9.55 (2.009)	29	-11.64 (2.054)	2.09 (-1.04, 5.21)

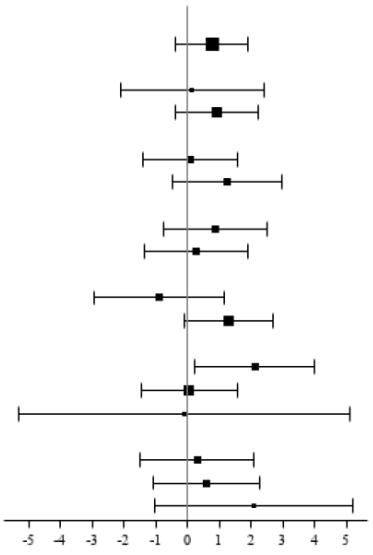


Figure 11. Forest Plot of Change from Baseline at Week 12 in ISS7 by Demographic Subgroup (mITT Set)

Impact of ADA on Clinical Outcome – efficacy

There were 30 patients who have post-treatment ADA positive results during Overall Period up to Week 24: 14/203 (6.9%), 8/205 (3.9%), 7/107 (6.5%), and 1/103 (1.0%) patients in CTP39 300, Xolair 300, CT-P39 150, and Xolair 150 treatment groups, respectively. Although it was difficult to observe any specific trends between the clinical outcome and ADA status due to the limited number of patients with ADA positive results in Study CT-P39 3.1, there was no apparent impact of ADAs on efficacy.

The following efficacy results in respect to change from baseline in weekly Itch Severity Score were reported (at week 12, mean values): Arm1 (300 mg CT-P39): -9.31, Arm 2-1 (300mg Xolair/CT-P39):

-10.00, Arm 2-2 (300mg Xolair/Xolair): -10.17, Arm 3 (CT-P39 150/300): -9.56, Arm 4 (Xolair 150/300): -8.73.

Summary of main efficacy results

The following table summarise the efficacy results from the main studies supporting the present application. The summary should be read in conjunction with the discussion on clinical efficacy as well as the biosimilarity assessment (see later sections).

Table 42: Summary of Efficacy for trial CT-P39 3.1

Title: A double-blind, randomized, active-controlled, parallel group, Phase 3 study to compare efficacy and safety of CT-P39 and Xolair in patients with chronic spontaneous urticaria who remain symptomatic despite H_1-antihistamine treatment.		
Study identifier	Protocol number: CT-P39 3.1 EudraCT number: 2020-000952-36	
Design	Randomized, parallel-group, double-blind, multicentre study	
	Duration of main phase:	Screening Period: within 28 days prior to the first study drug administration on Day 1 Treatment Period I: Study drug was given every 4 weeks up to Week 12 Treatment Period II: Study drug was given every 4 weeks up to Week 24 Follow-Up Period: up to Week 40, no study drug will be given
Hypothesis	To demonstrate that CT-P39 is equivalent to EU-approved Xolair in terms of efficacy	
Treatments arms	CT-P39 300 mg	Treatment Period I Arm 1 (CT-P39 300 mg group): 300 mg of CT-P39 was administered on Day 1 and repeated every 4 weeks (Week 0, 4, and 8) Number of randomized patients=204 Treatment Period II Arm 1 (CT-P39/CT-P39 group): 300 mg of CT-P39 was administered every 4 weeks (Week 12, 16, and 20) Number of randomized patients=187
	Xolair 300 mg	Treatment Period I Arm 2 (Xolair 300 mg group): 300 mg of EU-approved Xolair was administered on Day 1 and repeated every 4 weeks (Week 0, 4, and 8) Number of randomized patients=205 Treatment Period II Arm 2-1 (Xolair/CT-P39 group): 300 mg of CT-P39 was administered every 4 weeks (Week 12, 16, and 20) Number of randomized patients=96 Arm 2-2 (Xolair/Xolair group): 300 mg of EU-approved Xolair was administered every 4 weeks (Week 12, 16, and 20) Number of randomized patients=97
	CT-P39 150 mg	Treatment Period I Arm 3 (CT-P39 150 mg group): 150 mg of CT-P39 was

			administered on Day 1 and repeated every 4 weeks (Week 0, 4, and 8) Number of randomized patients=107 <u>Treatment Period II</u> Arm 3 (CT-P39 150/300 group): 300 mg of CT-P39 was administered every 4 weeks (Week 12, 16, and 20) Number of randomized patients=101
	Xolair 150 mg		<u>Treatment Period I</u> Arm 4 (Xolair 150 mg group): 150 mg of EU-approved Xolair was administered on Day 1 and repeated every 4 weeks (Week 0, 4, and 8) Number of randomized patients=103 <u>Treatment Period II</u> Arm 4 (Xolair 150/300 group): 300 mg of EU-approved Xolair was administered every 4 weeks (Week 12, 16, and 20) Number of randomized patients=98
Endpoints and definitions	Primary endpoint	Change from baseline in ISS7 of 300 mg of CT-P39 (Arm 1) and 300 mg of Xolair (Arm 2) at Week 12	ISS7: The sum of the daily itch severity score (ISS) over 7 days ranging from 0 to 21. ISS score is determined based on the severity of pruritus
	Secondary endpoints	Change from baseline in ISS7 at Weeks 8	
		Change from baseline in UAS7 at Weeks 8 and 12	UAS7: The sum of the daily urticaria activity score (UAS) over 7 days ranging from 0 to 42. The daily UAS (range 0-6) was calculated as the average of the sum of morning and evening scores of the two components: (1) ISS (range 0-3) and (2) HSS (range 0-3)
		Change from baseline in HSS7 at Weeks 8 and 12	HSS7: The sum of the daily hives severity score (HSS) over 7 days ranging from 0 to 21. HSS score is determined based on the number of hives
Database lock	20 Feb 2023 (for Week 24 clinical study report) 05 Jul 2023 (for Week 40 final clinical study report)		
<u>Results and Analysis</u>			
Analysis description	**Primary analysis**		
Analysis population and time point description	• Efficacy Population - *mITT Set:* The mITT Set was defined as all randomly assigned patients who received at least one full dose of either of the study drugs during Treatment Period I • The patient eDiary was given to patients at the first of Screening visit and completed twice daily by each patient until EOS. During the Screening Period, a patient was asked to complete the patient eDiary including UAS (ISS and HSS) twice daily for 7 consecutive days (Day -7 to Day -1) prior to the first study drug administration.		

Descriptive statistics and estimate variability	**Treatment group (mITT Set)**	**CT-P39 300 mg (N=203)**	**Xolair 300 mg (N=205)**
	n	186	192
	LS Mean (SE)	-9.21 (0.796)	-9.98 (0.798)
	Estimate of Treatment difference (95% CI)	0.77 (-0.37, 1.90)	
Analysis description	**Secondary analyses during Treatment Period I**		
Analysis population and time point description	Efficacy Population - *mITT Set:* The mITT Set was defined as all randomly assigned patients who received at least one full dose of either of the study drugs during Treatment Period I		
Descriptive statistics and estimate variability	**Analysis**	**CT-P39 300 mg (N=203)**	**Xolair 300 mg (N=205)**
	Change from baseline in ISS7 at Week 8		
	n	190	195
	LS Mean (SE)	-7.89 (0.811)	-8.81 (0.815)
	Estimate of Treatment difference (95% CI)	0.92 (-0.23, 2.07)	
	Change from baseline in UAS7 at Week 8		
	n	190	195
	LS Mean (SE)	-16.11 (1.617)	-18.00 (1.625)
	Estimate of Treatment difference (95% CI)	1.90 (-0.39, 4.19)	
	Change from baseline in UAS7 at Week 12		
	n	186	192
	LS Mean (SE)	-18.43 (1.597)	-19.86 (1.601)
	Estimate of Treatment difference (95% CI)	1.43 (-0.85, 3.70)	
	Change from baseline in HSS7 at Week 8		
	n	190	195
	LS Mean (SE)	-8.24 (0.854)	-9.21 (0.859)
	Estimate of Treatment difference (95% CI)	0.97 (-0.24, 2.18)	
	Change from baseline in HSS7 at Week 12		
	n	186	192
	LS Mean (SE)	-9.25 (0.844)	-9.89 (0.847)
	Estimate of Treatment difference (95% CI)	0.64 (-0.56, 1.85)	

2.6.5.3. Clinical studies in special populations

No specific studies considering children, elderly patients, patients with renal or hepatic impairment were conducted.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Efficacy data from Study CT-P39 3.1 were compared to the historical results from Xolair.

Table 43: Comparison of Efficacy between Study CT-P39 3.1 and Key Omalizumab Studies with Similar Design in CSU Patients

Efficacy Parameter Mean (SD) or Median (95% CI) or Percentage		Q4881g (Saini *et al.*, 2015)	Q4882g (Maurer *et al.*, 2013)	Study CT-P39 3.1	
		Omalizumab 300 mg (N=81)	Omalizumab 300 mg (N=79)	CT-P39 300 mg (N=203)	Xolair 300 mg (N=205)
Mean (SD)	Mean (SD) change from baseline in ISS7 at Week 12	-9.40 (5.73)	-9.8 (6.0)	-9.31 (6.20)	-9.99 (6.18)
	Mean (SD) change from baseline in UAS7 at Week 12	-20.75 (12.17)	-21.7 (12.8)	-19.27 (12.53)	-20.54 (12.69)
	Mean (SD) Change from baseline in HSS7 at Week 12	-11.35 (7.25)	-12.0 (7.6)	-9.96 (6.88)	-10.55 (6.93)
	Mean (SD) Change from baseline in DLQI at Week 12	-10.29 (7.23)	-10.2 (6.8)	-8.9 (7.5)	-9.0 (6.7)
	Mean (SD) change from baseline in Cu-Q_2oL at Week 12	N/A	-31.4 (N/A)	-25.40 (20.33)	-28.11 (19.93)
Median (95% CI)	Median (95% CI) time to MID response in ISS7 by Week 12 (in Weeks)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)
Percentage	Percentage of weekly itch severity score MID responders at Week 12	75.3%	78.5%	69.5%	74.1%
	Percentage of patients with UAS7 ≤ 6 at Week 12	N/A	65.8%	37.9%	40.5%
	Percentage of Complete Responders (UAS7 = 0) at Week 12	N/A	44.3%	23.6%	30.7%
Percentage (SD)	Percentage (SD) of angioedema-free days from Week 4 to Week 12 of therapy	96.1% (11.3%)	95.5% (14.5%)	93.47% (17.95%)	90.14% (25.64%)

2.6.5.6. Supportive studies

No additional supportive studies were provided.

No Human Factor (HF) studies were performed. Considering that the proposed device for CT-P39 PFS-S follows the configuration of the reference product device, Celltrion conducted a comparative analysis between CT-P39 PFS-S and EU approved Xolair to identify any unique risks in the device proposed for CT-P39 PFS-S and to determine whether a human factors study for CT-P39 PFS-S is necessary.

These comparative risk assessments of CT-P39 PFS-S and EU-approved Xolair show that there are no new risks introduced by the proposed device for CT-P39 PFS-S in comparison to the reference product.

In addition, Celltrion introduced a finger flange and changed the safety guard. In other aspects, the two devices have highly similar configurations.

Therefore, Celltrion concluded that a human factors study is not necessary for CT-P39 PFS-S and that the conclusions of the usability study on EU-approved Xolair are relevant and applicable to CT-P39 PFS-S. The approach as outlined above was broadly agreed during the SA EMEA/H/SA/4063/1/FU/1/2019/III.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development program encompasses a primary pharmacokinetic (PK) similarity study conducted in healthy subjects (study CT-P39 1.1) followed by a pivotal phase 3 therapeutic similarity study conducted in patients with chronic spontaneous urticaria (CSU) (study CT-P39 3.1). The proposed clinical development is considered acceptable since the clinical biosimilarity comparability exercise begin with a PK study and is followed by a clinical efficacy and safety trial and has considered the CHMP guidelines.

The study CT-P39 3.1 was designed to assess equivalence of CT-P39 to Xolair in patients with chronic spontaneous urticaria (CSU) who remain symptomatic despite H1-antihistamine treatment. The design of the pivotal study supporting this biosimilar application was discussed as a part of the scientific advice (SA) (EMEA/H/SA/4063/1/2019/III).

The main features of this trial were agreed during this SA including study population (patients with CSU who remain symptomatic despite H1-antihistamine treatment), primary and secondary endpoints and the equivalence margin for the primary endpoint (i.e. [-2.00, 2.00],).

In relation to the study population, it was agreed that patients with CSU are more homogenous and therefore a more sensitive population than population of patients with allergic asthma and therefore acceptable to be used in the pivotal efficacy study supporting this biosimilar application.

In addition, based on the mechanism of action of omalizumab (reducing IgE levels followed by downregulation of FcεRI) it was agreed that the data obtained in patients with CSU could be also used to support the asthma indication. An additional indication i.e chronic rhinosinusitis with nasal polyps (CRSwNP) was authorised for the reference product in 2020 and therefore was not discussed and agreed during the SA. However, taking into consideration the same mechanism of action of omalizumab and consistent PK profile across all the sought indications, the extrapolation from CSU to chronic rhinosinusitis with nasal polyps is considered justified.

Study design

The pivotal efficacy study provided in support of this application had 4 arms and two treatment period. Treatment period 1 (Week 1 to 12) for assessment of primary efficacy; and Treatment period II (Week 13 to 24) for assessment of long-term efficacy and safety.

Two dose level (150 mg and 300 mg) were tested. Arm 1 investigating 300 mg dose of CT-P39 and Arm 2 investigating 300 mg dose of Xolair are the primary interest of this application. Arm 3 investigating 150 mg dose of CT-P39 and Arm 4 investigating 150 mg of Xolair are not considered as pivotal as 150 mg dose is not approved in the EU for CSU and it is not applied for by the applicant.

After 12 weeks of treatment in the treatment period I patients were re-randomised and continued their treatment in the study for further 12 weeks in the treatment period 2. Patients in Arm 1 continued to receive 300 mg dose of CT-P39, whereas half of patients in Arm 2 (and originally receiving 300 mg dose of Xolair) were re-randomized to 300 mg dose of CT-P39 (Arm 2-1) and second half of these patients were continued to receive 300 mg dose of Xolair (Arm 2-2).

Patients in Arm 3 and 4 who were originally receiving a lower dose (150 mg) in the treatment period 2 received higher dose of the same product (CT-P39 and Xolair). As for treatment period 1 the efficacy data obtained in Arm 1 and 2 (Arm 2-1 and Arm 2-2) in treatment period 2 are of primary interest for this application.

For an EU MA, the most relevant comparison is between patients continuously treated with CT-P39 and patients who remained in EU-approved Xolair group after Week 12 (i.e. Arm 1 vs. Arm 2/Arm 2-2).

Main inclusion criteria

The inclusion criteria for this study were broadly agreed during the SA and they were similar to those used in the pivotal Xolair trials Q4881g and Q4882g with only small differences. As in the pivotal studies for Xolair patients were required to have CSU diagnosis (for at least 6 months prior to the first study drug administration) with the presence of hives associated with itching for ≥ 6 consecutive weeks despite current use of H1-antihistamine treatment for this time period. Weekly itch severity score required for enrolment was ≥ 8 points (in 0 to 21 points scale) and UAS7 was ≥ 16 points (in 0 to 42 points scale).

The exclusion criteria also were similar as used in the Xolair trials Q4881g and Q4882g. As expected, patients were restricted to those with spontaneous urticaria and therefore patients with chronic urticaria with clearly defined underlying etiology as well as those with any other active skin diseases associated with itch were excluded.

The use of any H2-antihistamine, LTRA, beta-blocker and doxepin prior to enrolment were prohibited. The maximum dose of H1-antihistamines was restricted.

Study treatment

Each patient received two SC injections per dosing day using a PFS during Treatment Periods I and II every four weeks (two 150 mg injections for the 300 mg dose level and one 150 mg of CT-P39 or Xolair plus placebo for the 150 mg dose level).

All patients were allowed to take one of the pre-defined nonsedating H1-antihistamines at approved dose throughout the study. Increasing the dose of the nonsedating H1-antihistamine treatment was not permitted.

Predefined nonsedating H1-antihistamines at approved dose, in addition to being used as background medication, was allowed as rescue therapy for itch relief on an as-needed basis throughout the study. The selection of the rescue medication was to be made once for an individual patient.

Study endpoints

Study objectives are considered appropriate to compare the clinical efficacy, safety and tolerability, PK and immunogenicity of proposed biosimilar CT-P39 and EU-approved Xolair.

The primary endpoint in the study was the change from baseline in ISS7 of 300 mg of CT-P39 (Arm 1) and 300 mg of Xolair (Arm 2) at Week 12. The change from baseline in the ISS is in-line with the primary endpoint from the Xolair CSU efficacy studies and is acceptable. The timing of the primary endpoint is also the same as used in the Q4881g and Q4882g studies.

Secondary endpoints were also similar to those investigated in the Xolair Q4881g and Q4882g studies and they included time to minimally important difference (MID; reduction of ≥ 5 points from baseline) response in ISS7 by Week 12, change from baseline in response in ISS7, percentage of MID responders in ISS7, the assessment of change from baseline in weekly urticaria activity score (UAS7), hives severity scores (HSS7), percentage of angioedema-free days and change from baseline in number of tablets/week of rescue therapy.

For most endpoints, the assessment was done at weeks 8, 12, and 24.

Audits and patient exclusions:

During pivotal study CT-P39 in patients with CSU, a total of 9 audits were conducted by Celltrion and/or the main CRO IQVIA, and the audits covered 7 out of 62 study sites that had 138 out of 634 (22%) patients enrolled in Study CT-P39 3.1. After the audits, a clinical site (Bulgaria) was terminated due to serious non-compliance. One critical, two major and two minor findings were identified from the audit, including inadequate source data management practice and lack of data reliability (see below).

GCP

Significant GCP non-compliances were found at one site during the study. For this site, the study team had detected unusual trends from reviewing eDiary compliance during the centralized monitoring and escalated the issue for investigation. The issues identified at the site included inadequate source data management practice and lack of data reliability. Also, PI's oversight on the site's data collection process was questionable taking all findings into consideration. These findings were deemed as serious non-compliance to the protocol and GCP. A total of 15 patients from the site were excluded from all the analysis sets, which is considered acceptable.

For one site, it was identified that 12 out of 19 patients had used 3 devices for eDiary entry during overlapping periods (23 September 2021-21 January 2022). Recruitment was put on hold and a Quality Issue (QI) investigation was conducted on 01 February 2022 to investigate how patients were physically completing the diary. Based on the outcome of the audits, Celltrion concluded that there was no sign of misconduct at the site and data reliability could be ensured.

Of note, the pivotal study was inspected by the EMA. The GCP IIR was circulated on 02 February 2024. The inspection team considered that the data submitted to the EMA are acceptable for the assessment of the application.

Efficacy data and additional analyses

A total of 634 patients were randomly assigned to the study drugs, and 619 patients were included in the RAN Set excluding 15 patients from one GCP noncompliant site (see further discussion below).

The majority of patient completed the treatment period 1 including 91.7% patients in Arm 1 (receiving 300 mg of CT-P39) and 93.7% in Arm 2 (receiving 300 mg Xolair). 40 patients discontinued the study treatment in Period 1, mostly in Arm 1 (16 patients) and Arm 2 (13 patients). The main reason for the treatment discontinuation was withdrawal of consent. In one patient each in Arm 1 and 2, disease progression was the reason for the treatment discontinuation.

A total of 579 patients underwent the second randomization process prior to the study drug administration at Week 12 (187 patients in Arm 1, 96 patients in Arm 2-1, 97 patients in Arm 2-2, 101 patients in Arm 3, and 98 patients in Arm 4).

In total, 181 patients received 24 weeks of treatment with 300 mg dose of CT-P39 and completed the treatment period 2. 94 patients received 24 weeks continued treatment with 300 mg of Xolair (patients in Arm1 in Period 1 and in Arm 2-2 in Period 2). Again, the most common reason for the treatment discontinuation in Period 2 was withdrawal of consent.

101 patients were recruited to the trial sites in Ukraine. Due to the war in Ukraine that occurred during the study, the sponsor implemented changes to the study conduct including temporary use of local laboratories and changes in the site monitoring visits. The reasons for these changes in the conduct of the study at sites in Ukraine are well understood. However, to further understand the potential impact of these changes on the study results, upon CHMP request, the applicant clarified, that only few patients were affected by changes introduced to the study conduct. In relation to the temporary use of local laboratory instead of central laboratory, this was applicable to 6 patients only. Further, among 101 patients enrolled in Ukraine, 86 patients had completed the Treatment Period I prior to the war, and only 15 (2.43%) patients had Week 12 visits scheduled after the war in Ukraine was started. Finally, the sensitivity analysis provided after excluding these 6 patients (3 patients in Arm 1 and 3 patients in Arm 2) who had Week 12 visits scheduled after the war in Ukraine, was consistent with the primary endpoint results.

Baseline characteristic of patients

The baseline characteristic of patients was similar across groups. The mean age of enrolled patients varied from 41.5 to 43.2 across the treatment groups. In line with the inclusion criteria, the minimum age of the enrolment was 12, the maximum 75. Most enrolled patients were female (>62% in any treatment group) and had baseline ISS7 ≥ 13 points (79% of patients). As required by the inclusion criteria all patients were taking antihistamines for systemic use prior to baseline. The second common prior medication was corticosteroids for systemic use followed by corticosteroids, dermatological preparations.

The treatment with nonsedating H1-antihistamine during the study was maintained by all except 1 patient (Arm 4) who switched to another background nonsedating H1-antihistamine during Treatment Period II. During the Treatment Period I there were no patients who had taken additional nonsedating H1- antihistamines in addition to the background nonsedating H1-antihistamine. A small percentage of patients (<3.2% in any treatment group) were taking additional nonsedating H1-antihistamines during the treatment period II. Rescue therapies were allowed during the study-period and it was analysed as a secondary endpoint.

All randomised patients with exception of one patient (Arm 1) were included in the in the mITT Set. One patient in Arm 1 who was randomised in error terminated the study prior to the first study drug administration.

Primary endpoint results

The primary endpoint in this study was a change from Baseline in Weekly Itch Severity Score of 300 mg of CT-P39 (Arm 1) and 300 mg of Xolair (Arm 2) assessed at Week 12.

Although a slightly better response and therefore lower ISS7 score was reported in patients receiving treatment with 300 mg Xolair, the 95% CI of treatment difference in the mean was [-0.37, 1.90] which was within the predefined equivalence margin of [-2.0, 2.0]. The primary endpoint results for the mITT population were consistent with those reported for the PP Set. In the PP set, the 95% CI of treatment difference in the mean change from baseline in ISS7 at Week 12 between 300 mg of CT-P39 and 300 mg of Xolair was [-0.45, 1.84]. The result of multiple imputation and tipping point analysis showed that missing data had no major impact on the result for the primary efficacy endpoint.

Secondary endpoint results-Treatment Period 1

Efficacy results in Arm 1 and 2 investigating 300 mg dose level.

Itch Severity Score

A change from baseline in the weekly Itch Severity Score investigated as a primary endpoint (at week 12) was also investigated at other times points. For this outcome measure at all timepoints except for Week 8, no treatment differences were observed. At week 8, the upper limit of the 95% CI was slightly higher than equivalence margin, i.e. (-0.23, 2.07), however, it could not be interpreted as evidence of a statistical difference when factoring in the multiplicity of analyses.

Other secondary endpoints

There was a consistent pattern of the secondary endpoints (mean change from baseline) across ISS7, HSS, and UAS. The difference between the treatment in secondary efficacy outcomes at Weeks 6, 8, 10, and 12 does not seem to be significant, except for some differences observed temporally in the percentage of responders at week 8 in ISS7 (63.5% vs. 72.7%; Diff.: -9.14%; 95%CI: -18.14% to -0.13%) and UAS of $\leqslant$ 6 at Week 8 (30% vs. 39.5%; Diff.: -9.46%; 95%CI: -18.66 to -0.27), which may have resulted from disease fluctuation. At week 12, these differences became non-significant.

Efficacy results for the lower dose level (150 mg)

For treatment period 1, the applicant also presented the efficacy results for the lower dose levels which were investigated in Arm 3 (150 mg of CT-P39) and Arm 4 (150 mg of Xolair). As 150 mg dose is not approved in the EU for CSU, this data is not considered pivotal in the context of the current application. Nevertheless, it is noted that for the majority efficacy endpoints investigated in the study, the efficacy results reported for 150 mg CT-P39 group were similar or better than those reported for 300mg CT-P39, which is unexpected finding. For example, at week 12, the mean (SD) changes from baseline in ISS7 was -9.31 (6.20) in the 300mg CT-P39 group and -9.56 (5.87) in the 150 mg CT-P39 group.

Therefore, the applicant was requested to comment on differences in the dose-response seen in CT-P39 in comparison to Xolair and discuss implications on the biosimilarity conclusion. Based on the provided additional analyses, it is agreed that the absence of the apparent dose-response in CT-P39 does not imply a treatment difference between CT-P39 and Xolair, considering the modest dose-response in Xolair and the compelling dose-relationship in PK and PD profiles. Further, it appears that the patients with low baseline IgE in CT P39 150 mg treatment group impacted on the overall results with their unexpected high responses, leading to the picture of a missing dose-response for CT-P39.

While some uncertainty whether CT-P39 exhibits the same dose response as seen for Xolair remains, taking into consideration the totality of the data, it is considered that this uncertainty should not preclude a positive conclusion on the biosimilarity between CT-P39 300 mg and Xolair 300 mg.

Of note, the mean C_{trough} of 300 mg CT-P39 and 300 mg EU-approved Xolair groups were higher, approximately double, compared to the mean serum concentrations of 150 mg CT-P39 and 150 mg EU-approved Xolair groups and for Xolair the efficacy results as expected were more favourable in the higher dose group (Arm 2) than in the lower dose group (Arm 4).

Secondary endpoint results-Treatment Period 2.

As discussed, after 12 weeks of treatment patients were re-randomised and continued their treatment in the study for further 12 weeks in the treatment period 2. Patients in Arm 1 continued to receive 300 mg dose of CT-P39, whereas half of patients in Arm 2 (and originally receiving 300 mg dose of Xolair) were re-randomized to 300 mg dose of CT-P39 (Arm 2-1) and second half of patients in this arm were continued to receive 300 mg dose of Xolair. Patients in Arm 3 and 4 who were originally receiving a lower dose (150 mg) in the treatment period 2 received higher dose of the same product (CT-P39 and

Xolair respectively). As for treatment period 1 the efficacy data obtained in Arm 1 and 2 (Arm 2-1 and Arm 2-2) in the treatment period 2 are of the primary interest for this application.

In all treatment arms, during the treatment period 2, clinical status of patients continued to improve with further decrease in Weekly Itch Severity Score, Weekly Urticaria Activity Score, Weekly Hives Severity Score and improvements in other corresponding endpoints.

For an EU MA, the most relevant comparison is between patients continuously treated with CT-P39 and patients who remained in EU-approved Xolair group after Week 12 (i.e. Arm 1 vs. Arm 2-2) however, the number of patients available for this assessment in Arm 2-2 is small and therefore these results need to be interpreted with caution.

For these patients, similar efficacy results were observed at week 24 for the most secondary endpoints including changes from baseline in ISS7 (-11.24 [6.23] points in Arm 1, -11.19 [5.88] points in Arm 2-2), change from baseline in Weekly Urticaria Activity Score (-23.12 [12.32] points in Arm 1, -23.55 [12.08] points in Arm 2-2), Percentage of Patients with Weekly Urticaria Activity Score of $\leqslant$ 6 points and Complete Responders in Weekly Urticaria Activity Score (102 [54.5%] patients and 75 [40.1%] patients in Arm 1, 46 [47.9%] patients and 36 [37.5%] patients in Arm 2-2), change from Baseline in the Weekly Hives Severity Score (-11.88 [6.73] points in Arm 1, and -12.36 [6.64] points in Arm 2-2).

Subgroup analysis

The applicant presented the subgroup analysis results for change from baseline at Week 12 in ISS7 in the subset of patients by age, gender, race (Asian, White), body weight (<80 kg, ≥80 kg), country, baseline ISS7, UAS7 and total IgE, presence of angioedema at baseline, duration of disease at baseline and the number of previous CSU medication. The applicant was requested to discuss results in Koreans and newly diagnosed patients and as in these subgroups treatment with CT-P39 seemed to be less favourable. As requested, the applicant presented the p-interaction values showing non-significant interaction by country and by duration of disease prior to baseline and therefore heterogeneity in response was not concluded.

ADA positive patients

There were 30 patients who have post-treatment ADA positive results up to Week 24: 14/203 (6.9%), 8/205 (3.9%), 7/107 (6.5%), and 1/103 (1.0%) patients in CTP39 300, Xolair 300, CT-P39 150, and Xolair 150 treatment groups, respectively. Based on the data provided, it is agreed there was no apparent impact of ADAs on efficacy as assessed at week 12.

2.6.7. Conclusions on the clinical efficacy

The primary endpoint of CT-P39 3.1 study was met. Although a slightly better response and therefore lower ISS7 score was reported in patients receiving treatment with 300 mg Xolair (at week 12 a change from baseline in ISS7 was - 9.98 in this group) as compared to those treated with 300 mg CT-P39 (at week 12 ISS7 was -9.21), the 95% CI of treatment difference in the mean was [-0.37, 1.90] which was within the predefined equivalence margin of [-2.0, 2.0]. From the efficacy point of view, the claim for the biosimilarity between CT-P39 and Xolair is supported.

2.6.8. Clinical safety

Safety and immunogenicity data on CT-P39 are available from two clinical studies (the pivotal PK study, Study CT-P39 1.1, and the confirmatory therapeutic equivalence study, Study CT-P39 3.1), where both were assessed as part of the secondary study objectives.

Study CT-P39 1.1 was conducted in healthy subjects following single dose administration and Study CT-P39 3.1 was conducted in patients with CSU following multiple dose administration. Thus, a single pooled safety analysis of both studies was not considered meaningful and safety results are discussed below per individual study.

Study CT-P39 3.1 was ongoing at the time of the initial MAA, and safety and immunogenicity data through Week 24 (EOT) only were provided in an interim Week 24 Clinical Study Report (CSR) at that time. The final CSR with full 40-week data from the Phase 3 study was submitted at Day 120 List of Questions during the MAA procedure. The study was completed on 27th April 2023, and the final CSR is dated 11th September 2023. The additional data are related to the 16-week Follow-Up Period post-treatment.

In both clinical studies, safety analyses were carried out using the safety population, which was defined (in both studies) as all randomly assigned subjects who received a full or partial dose of the study drug. In Study CT-P39 3.1, the "Safety Set" was defined as all randomly assigned patients who received at least 1 dose (full or partial) of either of the study drugs, and the "Safety-TP2" as all patients in Safety Set who received at least 1 dose (full or partial) of either of the study drugs during Treatment Period II.

Study CT-P39 3.1 consisted of a 4-week Screening Period followed by two treatment periods: Treatment Period I (TP1) with data from study drug administration at Weeks 0, 4 and 8 and treatment duration of 12 weeks, Treatment Period II (TP2) with data from study drug administration at Weeks 12, 16 and 20 and treatment duration of 12 weeks. Treatment Period II was followed by a 16-week Follow-Up Period, with visits scheduled Q4W until Week 40 (EOS). Safety data for Study CT-P39 3.1 are summarised by TP1 (Safety Set), TP2 (Safety-TP2 Subset), Follow-up Period and Overall Period.

Study CT-P39 1.1 consisted of two parts: Part 1 and Part 2 with study duration of 127 days. Safety data were summarised by the actual treatment group and presented separately for Part 1 and Part 2.

Safety assessments in both clinical studies included the following:

- Incidence and severity of adverse events (AEs), including serious adverse events (SAEs).
- Incidence and severity of adverse events of special interest (AESIs).
- Total and free serum IgE.
- Hypersensitivity monitoring.
- Vital sign assessments.
- Physical examination findings.
- Clinical laboratory analyses.

Immunogenicity, evaluated in the Safety Set, was assessed by means of monitoring development of ADAs and NAbs during both clinical studies.

2.6.8.1. Patient exposure

The overall safety database in support of this application included healthy subject exposed to single dose CT-P39 150 mg compared to EU-approved Xolair 150 mg in Study CT-P39 1.1 and CSU patients exposed to either CT-P39 (150 mg or 300 mg) or EU-approved Xolair (150 mg or 300mg) in Study CT-P39 3.1.

Study CT-P39 1.1: Healthy Subjects

Study CT-P39 1.1 provides safety data through Day 127. In total, 64 healthy adult subjects received a single dose of CT-P39 150 mg/ml s.c. in this study:

- In **Part 1**, 15 healthy subjects received a single dose of CT-P39 150 mg/ml s.c. and 15 received a single dose of EU-approved Xolair 150 mg/ml s.c.

- In **Part 2**, 49 healthy subjects received a single dose of CT-P39 150 mg/ml s.c. and 49 received a single dose of EU-approved Xolair 150 mg/ml s.c. A further 49 subjects received a single dose of US-licensed Xolair 150 mg/ml s.c.

Study CT-P39 3.1: CSU Patients

In Treatment Period I (TP1) of this study, a total of 618 patients received at least 1 dose. During Treatment Period II (TP2), a total of 578 patients received at least 1 dose of the study drug.

Overall, in Study CT-P39 3.1, a total of 178 patients received all 6 per protocol doses (6 months exposure) of CT-P39 300 mg, with 93 having received all 6 doses of EU-approved Xolair 300 mg. A total of 93, 98 and 93 patients received all 6 doses, as per protocol, in Arms 2-1 (switching), 3 (CT-P39 increasing) and 4 (EU-approved Xolair increasing) respectively.

In Study CT-P39 3.1, additional Arms 3 and 4 in TP1 (patients exposed to CT-P39 150 mg and EU-approved Xolair 150 mg, respectively, every 4 weeks up until Week 12) and Arms 2-1, 3 and 4 in TP2 (patients switched from EU-approved Xolair 300 mg s.c. to CT-P39 300 mg, and patients increased from CT-P39 150 mg or EU-approved Xolair 150 mg to CT-P39 300 mg or EU-approved Xolair 300 mg from Week 12 to 20) were incorporated into the study design to accommodate FDA requirements on the US-licensed 150 mg or 300 mg doses for treatment of CSU and proof of interchangeability.

A total of 554 patients entered the Follow-up Period and most patients completed the Follow-up Period and the study with 172/204 (84.3%) patients in the CT-P39 300 mg group, 172/205 (83.9%) patients in the Xolair 300 mg group (84/96 [87.5%] patients in the Xolair/CT-P39 group and 86/97 [88.7%] patients in the Xolair/Xolair group), 91/107 (85.0%) patients in the CT-P39 150 mg group and 83/103 (80.6%) patients in the Xolair 150 mg group.

2.6.8.2. Adverse events

Study CT-P39 1.1: Healthy Subjects

An overview of TEAEs reported from Parts 1 and 2 of Study CT-P39 1.1 are provided below:

Table 44: Overview of Treatment-Emergent Adverse Events in Study CT-P39 1.1: Safety Set

	Part 2			Part 1	
	CT-P39 (N=47)	EU-approved Xolair (N=49)	US-licensed Xolair (N=50)	CT-P39 (N=15)	EU-approved Xolair (N=15)
Total number of TEAEs	79	95	110	8	20
Number (%) of patients with ≥ 1 TEAE	33 (70.2)	37 (75.5)	34 (68.0)	6 (40.0)	9 (60.0)
Related	22 (46.8)	30 (61.2)	27 (54.0)	4 (26.7)	7 (46.7)
Unrelated	26 (55.3)	28 (57.1)	27 (54.0)	3 (20.0)	5 (33.3)
Number (%) of patients with ≥ 1 TEAE leading to death	0	0	0	0	0
Number (%) of patients with ≥ 1 TESAE	1 (2.1)	0	0	0	0
Related	0	0	0	0	0
Unrelated	1 (2.1)	0	0	0	0
Number (%) of patients with ≥ 1 TEAE leading to study discontinuation	0	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of allergic reaction type I/anaphylaxis	0	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of injection site reaction	8 (17.0)	5 (10.2)	6 (12.0)	1 (6.7)	1 (6.7)
Related	8 (17.0)	5 (10.2)	6 (12.0)	1 (6.7)	1 (6.7)
Unrelated	0	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of serum sickness/serum sickness-like reaction (type III hypersensitivity)	0	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of parasitic (helminth) infection	0	0	0	0	0
[redacted]					

Abbreviations: TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

In **Part 1** of Study CT-P39 1.1, TEAEs were reported for 6 (40.0%) and 9 (60.0%) subjects in the CT-P39 and EU-approved Xolair groups, respectively. The most frequently reported TEAEs by SOC were general disorders and administration site conditions (3 [20.0%] and 3 [20.0%] subjects, respectively) and nervous system disorders (1 [6.7%] and 5 [33.3%] subjects, respectively) and by PT was headache (1 [6.7%] and 5 [33.3%] subjects, respectively. No grade 3 or higher TEAEs were reported in Part 1. Related TEAEs were reported for 4 (26.7%) and 7 (46.7%) subjects in the CT-P39 and EU-approved Xolair groups, respectively. The most frequently reported related TEAE by SOC was nervous system disorders (1 [6.7%] and 5 [33.3%] subjects, respectively) and by PT was headache (1 [6.7%] and 5 [33.3%] subjects, respectively).

In **Part 2** of Study CT-P39 1.1, there was a similar incidence of TEAEs reported: 33 (70.2%), 37 (75.5%) and 34 (68.0%) subjects in the CT-P39, EU-approved Xolair and US-licensed Xolair groups, respectively. The most frequently reported TEAE by SOC was nervous system disorders (14 [29.8%], 14 [28.6%] and 20 [40.0%] subjects, respectively) and by PT was headache (11 [23.4%], 10 [20.4%] and 15 [30.0%] subjects, respectively). A higher incidence was reported for the TEAEs nausea (6 [12.8%] versus 2 [4.1%]) and injection site reaction (8 [17%] versus 5 [10.2%]) in the CT-P39 group when compared to the EU-approved Xolair group. However, it is likely that the small sample size in these groups might have contributed to the observed imbalance.

The majority of TEAEs were grade 1 or grade 2 in intensity, and grade 3 TEAEs were reported for one subject in each of CT-P39 group (head injury) and EU-approved Xolair group (syncope). Both were considered unrelated to the study drug.

The most frequently reported related TEAE by SOC was nervous system disorders (12 [25.5%], 9 [18.4%] and 13 [26.0%] subjects, respectively) and by PT was headache (9 [19.1%], 8 [16.3%] and 12 [24.0%] subjects, respectively).

Study CT-P39 3.1: CSU Patients

An overview of TEAEs reported from the Safety Set, Safety TP2 Subset, Follow-Up Period, and the Overall Period (up to Week 40/EOS) in Study CTP-39 3.1 is provided in the respective tables below:

Table 45: Overview of Treatment-Emergent Adverse Events in Study CT-P39 3.1 (Treatment Period I): Safety Set

	CT-P39 300 mg (N=203)	Xolair 300 mg (N=205)	CT-P39 150 mg (N=107)	Xolair 150 mg (N=103)
Total number of TEAEs	75	92	42	42
Number (%) of patients with ≥ 1 TEAE	52 (25.6)	54 (26.3)	29 (27.1)	28 (27.2)
Related	9 (4.4)	14 (6.8)	6 (5.6)	9 (8.7)
Unrelated	47 (23.2)	46 (22.4)	26 (24.3)	22 (21.4)
Number (%) of patients with ≥ 1 TEAE leading to death	0	0	0	0
Number (%) of patients with ≥ 1 TESAE	4 (2.0)	2 (1.0)	2 (1.9)	3 (2.9)
Related	2 (1.0)	0	1 (0.9)	0
Unrelated	2 (1.0)	2 (1.0)	1 (0.9)	3 (2.9)
Number (%) of patients with ≥ 1 TEAE leading to study drug discontinuation	3 (1.5)	2 (1.0)	0	0
Related	2 (1.0)	1 (0.5)	0	0
Unrelated	1 (0.5)	1 (0.5)	0	0
Number (%) of patients with ≥ 1 TEAE of allergic reaction Type I/anaphylaxis	0	1 (0.5)	0	0
Related	0	1 (0.5)	0	0
Unrelated	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of injection site reaction	5 (2.5)	9 (4.4)	1 (0.9)	3 (2.9)
Related	4 (2.0)	9 (4.4)	1 (0.9)	3 (2.9)
Unrelated	1 (0.5)	0	0	0
Number (%) of patients with ≥ 1 TEAE of serum sickness/serum sickness-like reaction (Type III hypersensitivity)	1 (0.5)	0	0	0
Related	1 (0.5)	0	0	0
Unrelated	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of parasitic (helminth) infection	0	0	0	0
[redacted]				

Abbreviations: TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

Table 46: Overview of Treatment-Emergent Adverse Events in Study CT-P39 3.1 (Treatment Period II): Safety-TP2 Subset

	CT-P39/ CT-P39 (N=187)	Xolair/ CT-P39 (N=96)	Xolair/ Xolair (N=96)	CT-P39 150/300 (N=101)	Xolair 150/300 (N=98)
Total number of TEAEs	78	35	43	31	25
Number (%) of patients with ≥ 1 TEAE	47 (25.1)	25 (26.0)	25 (26.0)	19 (18.8)	17 (17.3)
Related	8 (4.3)	7 (7.3)	4 (4.2)	1 (1.0)	6 (6.1)
Unrelated	41 (21.9)	19 (19.8)	22 (22.9)	18 (17.8)	13 (13.3)
Number (%) of patients with ≥ 1 TEAE leading to death	1 (0.5)	0	0	0	0
Related	0	0	0	0	0
Unrelated	1 (0.5)	0	0	0	0
Number (%) of patients with ≥ 1 TESAE	5 (2.7)	0	2 (2.1)	0	0
Related	1 (0.5)	0	0	0	0
Unrelated	4 (2.1)	0	2 (2.1)	0	0
Number (%) of patients with ≥ 1 TEAE leading to study drug discontinuation	1 (0.5)	0	0	0	0
Related	1 (0.5)	0	0	0	0
Unrelated	0	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of allergic reaction Type I/anaphylaxis	0	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of injection site reaction	1 (0.5)	3 (3.1)	2 (2.1)	1 (1.0)	1 (1.0)
Related	1 (0.5)	3 (3.1)	1 (1.0)	1 (1.0)	1 (1.0)
Unrelated	0	0	1 (1.0)	0	0
Number (%) of patients with ≥ 1 TEAE of serum sickness/serum sickness-like reaction (Type III hypersensitivity)	1 (0.5)	0	0	0	0
Related	1 (0.5)	0	0	0	0
Unrelated	0	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of parasitic (helminth) infection	0	0	0	0	0

Abbreviations: TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

Table 47: Overview of Treatment-Emergent Adverse Events in Study CT-P39 3.1 (Follow-up Period): Safety Set and Safety TP2 Subset

	CT-P39 300 mg (N=203)	Xolair 300 mg (N=205)	Xolair/ CT-P39[1] (N=96)	Xolair/ Xolair[1] (N=96)	CT-P39 150 mg (N=107)	Xolair 150 mg (N=103)
Total number of TEAEs	49	50	28	21	35	23
Number (%) of patients with ≥ 1 TEAE	37 (18.2)	39 (19.0)	19 (19.8)	19 (19.8)	24 (22.4)	20 (19.4)
Related	1 (0.5)	0	0	0	0	1 (1.0)
Unrelated	36 (17.7)	39 (19.0)	19 (19.8)	19 (19.8)	24 (22.4)	19 (18.4)
Number (%) of patients with ≥ 1 TEAE leading to death	0	0	0	0	0	0
Number (%) of patients with ≥ 1 TESAE	1 (0.5)	4 (2.0)	3 (3.1)	1 (1.0)	3 (2.8)	0
Related	0	0	0	0	0	0
Unrelated	1 (0.5)	4 (2.0)	3 (3.1)	1 (1.0)	3 (2.8)	0
Number (%) of patients with ≥ 1 TEAE leading to study drug discontinuation	0	0	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of allergic reaction Type I/anaphylaxis	0	0	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of injection site reaction	0	0	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of serum sickness/serum sickness-like reaction (Type III hypersensitivity)	0	0	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of parasitic (helminth) infection	0	0	0	0	0	0
[redacted]						

Note: Events reported from the CT-P39 300 mg, Xolair 300 mg, CT-P39 150 mg and Xolair 150 mg groups are summarized using the Safety Set and the Xolair/CT-P39 and Xolair/Xolair groups are summarized using the Safety-TP2 Subset.

[1] Based on patients who were randomized to Xolair for TP1 then re-randomized to CT-P39 or Xolair prior to TP2. The number of patients may not add up to overall numbers in the Xolair 300 mg group due to discontinuation prior to TP2.

Abbreviations: TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; TP1, Treatment Period I; TP2, Treatment Period II

Table 48: Overview of Treatment-Emergent Adverse Events in Study CT-P39 3.1 (Overall Period): Safety Set and Safety TP2 Subset

	CT-P39 300 mg (N=203)	Xolair 300 mg (N=205)	Xolair/ CT-P39[1] (N=96)	Xolair/ Xolair[1] (N=96)	CT-P39 150 mg (N=107)	Xolair 150 mg (N=103)
Total number of TEAEs	203	223	107	108	108	90
Number (%) of patients with ≥ 1 TEAE	89 (43.8)	99 (48.3)	48 (50.0)	47 (49.0)	53 (49.5)	50 (48.5)
Related	17 (8.4)	22 (10.7)	12 (12.5)	9 (9.4)	7 (6.5)	14 (13.6)
Unrelated	81 (39.9)	89 (43.4)	41 (42.7)	45 (46.9)	50 (46.7)	44 (42.7)
Number (%) of patients with ≥ 1 TEAE leading to death	1 (0.5)	0	0	0	0	0
Related	0	0	0	0	0	0
Unrelated	1 (0.5)	0	0	0	0	0
Number (%) of patients with ≥ 1 TESAE	9 (4.4)	6 (2.9)	3 (3.1)	2 (2.1)	4 (3.7)	3 (2.9)
Related	3 (1.5)	0	0	0	1 (0.9)	0
Unrelated	6 (3.0)	6 (2.9)	3 (3.1)	2 (2.1)	3 (2.8)	3 (2.9)
Number (%) of patients with ≥ 1 TEAE leading to study drug discontinuation	4 (2.0)	2 (1.0)	0	0	0	0
Related	3 (1.5)	1 (0.5)	0	0	0	0
Unrelated	1 (0.5)	1 (0.5)	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of allergic reaction Type I/anaphylaxis	0	1 (0.5)	0	0	0	0
Related	0	1 (0.5)	0	0	0	0
Unrelated	0	0	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of injection site reaction	5 (2.5)	12 (5.9)	6 (6.3)	5 (5.2)	2 (1.9)	3 (2.9)
Related	4 (2.0)	11 (5.4)	6 (6.3)	4 (4.2)	2 (1.9)	3 (2.9)
Unrelated	1 (0.5)	1 (0.5)	0	1 (1.0)	0	0
Number (%) of patients with ≥ 1 TEAE of serum sickness/serum sickness-like reaction (Type III hypersensitivity)	2 (1.0)	0	0	0	0	0
Related	2 (1.0)	0	0	0	0	0
Unrelated	0	0	0	0	0	0
Number (%) of patients with ≥ 1 TEAE of parasitic (helminth) infection	0	0	0	0	0	0

[redacted]

Note: Events reported from the CT-P39 300 mg, Xolair 300 mg, CT-P39 150 mg and Xolair 150 mg groups are summarized using the Safety Set and the Xolair/CT-P39 and Xolair/Xolair groups are summarized using the Safety-TP2 Subset.
[1] Based on patients who were randomized to Xolair for TP1 then re-randomized to CT-P39 or Xolair prior to TP2. The number of patients may not add up to overall numbers in the Xolair 300 mg group due to discontinuation prior to TP2.
Abbreviations: TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; TP1, Treatment Period I; TP2, Treatment Period II

The most frequently reported TEAEs, those reported for ≥ 2% of patients in any of the treatment arms, at the PT level during the Overall Period are summarised in the table below:

Table 49: TEAEs by PT Reported for at least 2% of Patients in Any Treatment Group by SOC and PT in Study CT-P39 3.1 (Overall Period): Safety Set and Safety- TP2 Subset

System Organ Class Preferred Term	CT-P39 300 mg (N=203)	Xolair 300 mg (N=205)	Xolair/ CT-P39[1] (N=96)	Xolair/ Xolair[1] (N=96)	CT-P39 150 mg (N=107)	Xolair 150 mg (N=103)
Number (%) of patients with ≥ 1 TEAE	**89 (43.8)**	**99 (48.3)**	**48 (50.0)**	**47 (49.0)**	**53 (49.5)**	**50 (48.5)**
Cardiac disorders	**3 (1.5)**	**3 (1.5)**	**1 (1.0)**	**2 (2.1)**	**1 (0.9)**	**0**
Palpitations	0	2 (1.0)	0	2 (2.1)	0	0
Gastrointestinal disorders	**16 (7.9)**	**14 (6.8)**	**10 (10.4)**	**4 (4.2)**	**6 (5.6)**	**5 (4.9)**
Constipation	0	2 (1.0)	2 (2.1)	0	0	0
Diarrhoea	4 (2.0)	4 (2.0)	2 (2.1)	2 (2.1)	0	0
General disorders and administration site conditions	**15 (7.4)**	**18 (8.8)**	**10 (10.4)**	**7 (7.3)**	**6 (5.6)**	**6 (5.8)**
Chills	0	2 (1.0)	2 (2.1)	0	0	0
Injection site reaction	5 (2.5)	12 (5.9)	6 (6.3)	5 (5.2)	2 (1.9)	3 (2.9)
Immune system disorders	**3 (1.5)**	**4 (2.0)**	**1 (1.0)**	**2 (2.1)**	**4 (3.7)**	**0**
Immunisation reaction	0	2 (1.0)	0	2 (2.1)	1 (0.9)	0
Infections and infestations	**48 (23.6)**	**56 (27.3)**	**26 (27.1)**	**28 (29.2)**	**26 (24.3)**	**22 (21.4)**
COVID-19	12 (5.9)	18 (8.8)	9 (9.4)	9 (9.4)	10 (9.3)	10 (9.7)
Gingivitis	2 (1.0)	2 (1.0)	2 (2.1)	0	0	0
Nasopharyngitis	11 (5.4)	14 (6.8)	5 (5.2)	8 (8.3)	9 (8.4)	3 (2.9)
Tonsillitis	3 (1.5)	4 (2.0)	3 (3.1)	1 (1.0)	0	0
Upper respiratory tract infection	4 (2.0)	5 (2.4)	1 (1.0)	4 (4.2)	5 (4.7)	2 (1.9)
Musculoskeletal and connective tissue disorders	**13 (6.4)**	**16 (7.8)**	**8 (8.3)**	**8 (8.3)**	**6 (5.6)**	**6 (5.8)**
Arthralgia	5 (2.5)	4 (2.0)	4 (4.2)	0	2 (1.9)	2 (1.9)
Back pain	3 (1.5)	3 (1.5)	1 (1.0)	2 (2.1)	1 (0.9)	1 (1.0)
Myalgia	3 (1.5)	2 (1.0)	0	2 (2.1)	1 (0.9)	1 (1.0)
Nervous system disorders	**11 (5.4)**	**12 (5.9)**	**3 (3.1)**	**8 (8.3)**	**7 (6.5)**	**8 (7.8)**
Dizziness	0	0	0	0	4 (3.7)	2 (1.9)
Headache	8 (3.9)	6 (2.9)	1 (1.0)	5 (5.2)	3 (2.8)	6 (5.8)
Respiratory, thoracic and mediastinal disorders	**3 (1.5)**	**8 (3.9)**	**1 (1.0)**	**7 (7.3)**	**3 (2.8)**	**0**
Asthma	0	2 (1.0)	0	2 (2.1)	1 (0.9)	0
Rhinitis allergic	0	2 (1.0)	0	2 (2.1)	1 (0.9)	0
Vascular disorders	**3 (1.5)**	**4 (2.0)**	**2 (2.1)**	**2 (2.1)**	**5 (4.7)**	**1 (1.0)**
Hypertension	3 (1.5)	3 (1.5)	2 (2.1)	1 (1.0)	5 (4.7)	1 (1.0)

[redacted]

Note: Events reported from the CT-P39 300 mg, Xolair 300 mg, CT-P39 150 mg and Xolair 150 mg groups are summarized using the Safety Set and the Xolair/CT-P39 and Xolair/Xolair groups are summarized using the Safety-TP2 Subset.
At each level of summarization, patients are counted once if they reported one or more events.
[1] Based on patients who were randomized to Xolair for TP1 then re-randomized to CT-P39 or Xolair prior to TP2. The number of patients may not add up to overall numbers in the Xolair 300 mg group due to discontinuation prior to TP2.
Abbreviations: PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event; TP1, Treatment Period I; TP2, Treatment Period II

Based on data submitted through Week 40 (EOS), during the Overall Period, TEAEs were reported for 89 (43.8%) patients in the CT-P39 300 mg group, 99 (48.3%) patients in the Xolair 300 mg group, 48 (50.0%) patients in the Xolair/CT-P39 group, 47 (49.0%) patients in the Xolair/Xolair group, 53 (49.5%) patients in the CT-P39 150 mg group and 50 (48.5%) patients in the Xolair 150 mg group. The most frequently reported TEAE by SOC was infections and infestations (48 [23.6%], 56 [27.3%],

26 [27.1%], 28 [29.2%], 26 [24.3%] and 22 [21.4%] patients in the CT-P39 300 mg, Xolair 300 mg, Xolair/CT-P39, Xolair/Xolair, CT-P39 150 mg and Xolair 150 mg groups, respectively) and by PT was COVID-19 (12 [5.9%], 18 [8.8%], 9 [9.4%], 9 [9.4%], 10 [9.3%] and 10 [9.7%] patients, respectively).

The proportion of patients with at least 1 TEAE was comparable between the treatment groups, regardless of the study drug, dosage, switching treatment or increasing dosage.

During the Overall Period, related TEAEs were reported for 17 (8.4%) patients in the CT-P39 300 mg group, 22 (10.7%) patients in the Xolair 300 mg group, 12 (12.5%) patients in the Xolair/CT-P39 group, 9 (9.4%) patients in the Xolair/Xolair group, 7 (6.5%) patients in the CT-P39 150 mg group and 14 (13.6%) patients in the Xolair 150 mg group. The most frequently reported related TEAE by SOC was general disorders and administration site conditions (7 [3.4%], 14 [6.8%], 9 [9.4%], 4 [4.2%], 3 [2.8%] and 5 [4.9%] patients in the CT-P39 300 mg, Xolair 300 mg, Xolair/CT-P39, Xolair/Xolair, CT-P39 150 mg and Xolair 150 mg groups, respectively) and by PT was injection site reaction (4 [2.0%], 11 [5.4%], 6 [6.3%], 4 [4.2%], 2 [1.9%] and 3 [2.9%] patients, respectively).

The majority of TEAEs during the Overall Period were grade 1 or grade 2 in intensity. During the Overall Period, grade 3 or higher TEAEs were reported for 11 (5.4%) patients in the CT-P39 300 mg group, 9 (4.4%) patients in the Xolair 300 mg group, 6 (6.3%) patients in the Xolair/CT-P39 group, 2 (2.1%) patients in the Xolair/Xolair group, 7 (6.5%) patients in the CT-P39 150 mg group and 6 (5.8%) patients in the Xolair 150 mg group. Other than blood creatine phosphokinase increased reported for 2 patients in the Xolair 300 mg group, there were no grade 3 or higher TEAEs by PT reported for more than 1 patient within any of the treatment group (although COVID-19 and coronavirus infection, which were captured under different PTs, were reported in 1 [1.0%] patient each in the Xolair 150 mg group).

2.6.8.3. Serious adverse event/deaths/other significant events

Study CT-P39 1.1: Healthy Subjects

Deaths

There were no deaths reported in either part of Study CT-P39 1.1.

Serious Adverse Events

There was 1 TESAE reported in Part 2 and there were no TESAEs in Part 1. The grade 3 TESAE (head injury) occurred in the CT-P39 arm as a result of an assault. It was not considered related in the study drug.

Adverse Events of Special Interest

No TEAESIs classified as allergic reaction Type I/anaphylaxis, serum sickness/serum sickness-like reaction (Type III hypersensitivity) or parasitic (helminth) infection were reported in either Part 2 and Part 1 of the study.

The only reported TEAESIs were injection site reactions. In Part 1, injection site reactions were reported for 1 (6.7%) subject in the CT-P39 group and 1 (6.7%) subject in the EU-approved Xolair group. Both events were grade 1 in intensity, non-serious, and did not lead to study discontinuation. Both subjects have recovered from the events.

Injection site reactions reported in Part 2 are summarised below:

Table 50: Summary of Injection Site Reaction in Study CT-P39 1.1 Part 2: Safety Set

	CT-P39 (N=47)	EU-approved Xolair (N=49)	US-licensed Xolair (N=50)
Total number of injection site reactions	**8**	**5**	**6**
Number (%) of patients with ≥ 1 injection site reaction	**8 (17.0)**	**5 (10.2)**	**6 (12.0)**
Related	8 (17.0)	5 (10.2)	6 (12.0)
Grade 1	8 (17.0)	5 (10.2)	6 (12.0)

[redacted]

Note: At each level of summarization, patients are counted once if they reported one or more events. Only the most severe event is counted.

Study CT-P39 3.1: CSU Patients

Death

There was one death reported in Study CT-P39 3.1 in Arm 1 (CT-P39 300 mg/CT-P39 300 mg) of TP2. The reported reason for death was due to the SAE of completed suicide, which was considered to be unrelated to the study drug by the investigator:

A 39-year-old white male from Arm 1 (CT-P39 300 mg) died due to a completed suicide. The event occurred 3 days after the patient received the Week 20 dose of the study drug. The patient had been under constant control of a psychiatric out-patient clinic and had been on stable doses of duloxetine hydrochloride and carbamazepine for the medical history of personality disorder. The event was considered by the Investigator to be unrelated to the study drug as it was considered an individual event.

Serious Adverse Events

SAEs reported during TP1 and TP2, respectively, are tabulated below by SOC and PT, with severity and relatedness assigned:

Table 51: TESAEs by SOC and PT in Study CT-P39 3.1 (Treatment Period I): Safety Set

System Organ Class Preferred Term	CT-P39 300 mg (N=203)	Xolair 300 mg (N=205)	CT-P39 150 mg (N=107)	Xolair 150 mg (N=103)
Number (%) of patients with ≥ 1 TESAE	**4 (2.0)**	**2 (1.0)**	**2 (1.9)**	**3 (2.9)**
Cardiac disorders	**1 (0.5)**	**0**	**0**	**0**
Myocardial ischaemia - Grade 3, Related	1 (0.5)	0	0	0
Gastrointestinal disorders	**1 (0.5)**	**0**	**0**	**1 (1.0)**
Colitis - Grade 3, Unrelated	1 (0.5)	0	0	0
Femoral hernia - Grade 3, Unrelated	0	0	0	1 (1.0)

System Organ Class Preferred Term	CT-P39 300 mg (N=203)	Xolair 300 mg (N=205)	CT-P39 150 mg (N=107)	Xolair 150 mg (N=103)
General disorders and administration site conditions	**1 (0.5)**	**0**	**0**	**0**
Oedema peripheral - Grade 3, Related	1 (0.5)	0	0	0
Infections and infestations	**0**	**1 (0.5)**	**0**	**2 (1.9)**
COVID-19 - Grade 3, Unrelated	0	0	0	1 (1.0)
Chronic tonsillitis - Grade 2, Unrelated	0	1 (0.5)	0	0
Coronavirus infection - Grade 3, Unrelated	0	0	0	1 (1.0)
Investigations	**0**	**0**	**1 (0.9)**	**0**
Tryptase increased - Grade 2, Related	0	0	1 (0.9)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**0**	**2 (1.0)**	**0**	**0**
Papillary thyroid cancer - Grade 3, Unrelated	0	1 (0.5)	0	0
Ureteric cancer - Grade 2, Unrelated	0	1 (0.5)	0	0
Reproductive system and breast disorders	**1 (0.5)**	**0**	**1 (0.9)**	**0**
Menometrorrhagia - Grade 3, Unrelated	1 (0.5)	0	0	0
Vaginal haemorrhage - Grade 3, Unrelated	0	0	1 (0.9)	0

[redacted]

Note: At each level of summarization, patients are counted once if they reported one or more events.
Abbreviations: PT, preferred term; SOC, system organ class; TESAE, treatment-emergent serious adverse event

Table 52: TESAEs by SOC and PT in Study CT-P39 3.1 (Treatment Period II): Safety-TP2 Subset

System Organ Class Preferred Term	CT-P39/ CT-P39 (N=187)	Xolair/ CT-P39 (N=96)	Xolair/ Xolair (N=96)	CT-P39 150/300 (N=101)	Xolair 150/300 (N=98)
Number (%) of patients with ≥ 1 TESAE	**5 (2.7)**	**0**	**2 (2.1)**	**0**	**0**
Gastrointestinal disorders	**1 (0.5)**	**0**	**0**	**0**	**0**
Haemorrhoids - Grade 3, Unrelated	1 (0.5)	0	0	0	0
Infections and infestations	**0**	**0**	**1 (1.0)**	**0**	**0**
Appendicitis - Grade 2, Unrelated	0	0	1 (1.0)	0	0
Injury, poisoning and procedural complications	**1 (0.5)**	**0**	**0**	**0**	**0**
Radius fracture - Grade 3, Unrelated	1 (0.5)	0	0	0	0

System Organ Class Preferred Term	CT-P39/ CT-P39 (N=187)	Xolair/ CT-P39 (N=96)	Xolair/ Xolair (N=96)	CT-P39 150/300 (N=101)	Xolair 150/300 (N=98)
Musculoskeletal and connective tissue disorders	**1 (0.5)**	**0**	**0**	**0**	**0**
Arthropathy - Grade 2, Related	1 (0.5)	0	0	0	0
Psychiatric disorders	**1 (0.5)**	**0**	**0**	**0**	**0**
Completed suicide - Grade 5, Unrelated	1 (0.5)	0	0	0	0
Reproductive system and breast disorders	**1 (0.5)**	**0**	**0**	**0**	**0**
Menometrorrhagia - Grade 3, Unrelated	1 (0.5)	0	0	0	0
Vascular disorders	**0**	**0**	**1 (1.0)**	**0**	**0**
Behcet's syndrome - Grade 3, Unrelated	0	0	1 (1.0)	0	0

[redacted]

Note: At each level of summarization, patients are counted once if they reported one or more events.
Abbreviations: PT, preferred term; SOC, system organ class; TESAE, treatment-emergent serious adverse event

During the Follow-up Period, TESAEs were reported for 1 (0.5%) patient in the CT-P39 300 mg group, 4 (2.0%) patients in the Xolair 300 mg group, 3 (3.1%) patients in the Xolair/CT-P39 group, 1 (1.0%) patient in the Xolair/Xolair group, 3 (2.8%) patients in the CT-P39 150 mg group and none in the Xolair 150 mg group. All TESAEs were considered unrelated to the study drug and there were no TESAEs by PT that were reported for more than 1 patient within any of the treatment group.

During the Overall Period, TESAEs were reported for 9 (4.4%) patients in the CT-P39 300 mg group, 6 (2.9%) patients in the Xolair 300 mg group, 3 (3.1%) patients in the Xolair/CT-P39 group, 2 (2.1%) patients in the Xolair/Xolair group, 4 (3.7%) patients in the CT-P39 150 mg group and 3 (2.9%) patients in the Xolair 150 mg group. There were no TESAEs by PT that were reported for more than 1 patient within any of the treatment group (although COVID-19 and coronavirus infection, which were captured under different PTs, were reported in 1 [1.0%] patient each in the Xolair 150 mg group).

Of the TESAEs reported in the study, four were considered possibly related to the study drug. All four were reported in the CT-P39 study arms: In TP1, two in Arm 1 (CT-P39 300 mg) of TP1, one in Arm 3 (CT-P39 150 mg), and one in Arm 1 (CT-P39 300 mg/ CT-P39 300 mg) of TP2.

Of these four TESAEs, two were of grade 3 severity. Both events (myocardial ischaemia and oedema peripheral) resulted in withdrawal of the study drug and treatment with medication. Both events were reported as resolved.

In the reported TESAE of myocardial ischaemia, in a 53-year-old male patient no prior diagnosis of acute coronary syndrome or ischemic heart disease had been made.

In the reported TESAE of oedema peripheral, the investigator assessed the event as possibly related to the study drug since temporal relationship could not be ruled out, but overlapping confounding factors were identified (starting hormonal contraception for the first time, COVID-19 vaccination and risk factors of obesity, and history of smoking).

Of the grade 2 related TESAE reported in the CT-P39 groups, one (tryptase increased) occurred in the 150 mg arm in a patient with a medical history of increased tryptase, and one (arthropathy) occurred in TP2 CT-P39 300mg group. The former was ongoing at EOS. The latter had resolved.

Adverse Events of Special Interest

Allergic reaction type I/anaphylaxis

One TEAESI of allergic reaction type I/anaphylaxis was reported during the overall study. It was reported in the Xolair 300 mg group of TP1 as grade 2 non-serious TEAE of type I hypersensitivity

(SOC immune system disorders) with signs and symptoms of nausea and rash. It was considered related in the study drug.

Injection site reaction

The following injection site reactions were reported in the Overall Period:

Table 53: Summary of Injection Site Reaction in Study CT-P39 3.1 (Overall Period): Safety Set and Safety-TP2 Subset

	CT-P39 300 mg (N=203)	Xolair 300 mg (N=205)	Xolair/ CT-P39[1] (N=96)	Xolair/ Xolair[1] (N=96)	CT-P39 150 mg (N=107)	Xolair 150 mg (N=103)
Total number of injection site reactions	**6**	**20**	**10**	**9**	**2**	**5**
Number (%) of patients with ≥ 1 injection site reaction	**5 (2.5)**	**12 (5.9)**	**6 (6.3)**	**5 (5.2)**	**2 (1.9)**	**3 (2.9)**
Related	4 (2.0)	11 (5.4)	6 (6.3)	4 (4.2)	2 (1.9)	3 (2.9)
Grade 1	4 (2.0)	8 (3.9)	5 (5.2)	3 (3.1)	2 (1.9)	2 (1.9)
Grade 2	0	3 (1.5)	1 (1.0)	1 (1.0)	0	1 (1.0)
Unrelated	1 (0.5)	1 (0.5)	0	1 (1.0)	0	0
Grade 1	1 (0.5)	0	0	0	0	0
Grade 2	0	1 (0.5)	0	1 (1.0)	0	0

Note: Events reported from the CT-P39 300 mg, Xolair 300 mg, CT-P39 150 mg and Xolair 150 mg groups are summarized using the Safety Set and the Xolair/CT-P39 and Xolair/Xolair groups are summarized using the Safety-TP2 Subset.
At each level of summarization, patients are counted once if they reported one or more events.
[1] Based on patients who were randomized to Xolair for TP1 then re-randomized to CT-P39 or Xolair prior to TP2. The number of patients may not add up to overall numbers in the Xolair 300 mg group due to discontinuation prior to TP2.
Abbreviations: TP1, Treatment Period I; TP2, Treatment Period II

Allergic Reaction Type III (Serum Sickness/Serum Sickness-Like Reaction)

There were two reported cases of allergic reaction Type III (Serum Sickness/Serum Sickness-Like Reaction). Both were reported in different patients in CT-P39 arms as grade 2 non-serious TEAE of type III immune complex mediated reaction (SOC immune system disorders) and were considered possibly related to the study drug.

In TP1, Arm 1 (CT-P39 300 mg), the event was reported 3 days after Week 0 administration. No action was taken with the study drug following the event and the patient received medical treatment for the event. Additional complement tests were conducted after the start of this event and did not show elevations of C3 and C4, while CH50 was elevated at Screening and during additional testing. The patient's ADA status was negative until Week 24, where it converted to positive (ADA titre: 50).

In TP2, Arm 1(CT-P39 300 mg/ CT-P39 300 mg), the event was reported 1 day after Week 20 administration. Action with the study drug was not applicable as the patient completed the scheduled study drug administration up to Week 20 and continued with study participation following the event. The patient received medical treatment for the event. Additional complement tests were conducted after the start of this event and did not show elevations of C3 and C4, while CH50 was elevated at Screening and during additional testing. The patient's ADA status was negative throughout the study.

Parasitic (helminth) infection

There were no TEAESIs classified as parasitic (helminth) infections during the studied period.

Malignancy

Malignancy was reported for two patients from the Xolair 300 mg group. One patient was reported with a grade 3 TESAE of papillary thyroid cancer, which was considered unrelated to the study drug, during

TP1. The patient discontinued the study drug due to the event and recovered after surgery. One patient was reported with a grade 2 TESAE of ureteric cancer, which was considered unrelated to the study drug during TP1. Then it was upgraded to a grade 3 TESAE during the Follow-up Period as the patient was re-hospitalized for surgical treatment. No action was taken with the study drug as all study drug administration was completed and the patient is recovering after surgery.

2.6.8.4. Laboratory findings

Clinical Laboratory Evaluations:

In Studies CT-P39 1.1 and CT-P39 3.1, most laboratory parameters had no CTCAE grade (e.g., the post-baseline laboratory result did not satisfy any CTCAE grade criteria) or were CTCAE Grade 1 (mild) or Grade 2 (moderate) with transient changes over time.

The most common higher laboratory parameter observed in both studies (both parts of the phase 1 and both treatment periods of the phase 3 study) was CPK increased. A grade 4 increased CPK in the CT-P39 arm of TP1 in Study CT-P39 3.1 was reported as a TEAE and considered unrelated to the study drug. All reported increased CPK abnormal laboratory parameters were considered as non-cardiac as subjects showed non-clinically significant abnormal ECG during the study. Patients in the phase 3 study showed normal CK-MB levels throughout the study.

During the Follow-Up Period, the majority of laboratory parameters had no CTCAE grade (ie, the post-baseline laboratory result did not satisfy any CTCAE grade criteria) or were CTCAE Grade 1 (mild) or Grade 2 (moderate) for each laboratory parameter. In general, there was no notable difference between all treatment arms for patients with any grade of CTCAE in laboratory parameters. Two patients (one who had completed study drug administration but didn't enter the Follow-Up Period) reported Grade 4 CPK increased at Week 40 (EOS). Neither were considered as a cardiac issue since the patients showed normal ECG and CK-MB level during the study participation. There was no reported TEAE.

Vital signs, physical findings and other observations related to safety:

Changes from baseline were small for vital signs and body weight and no notable shifts from baseline were observed for hypersensitivity monitoring, ECG and physical examination.

There were no notable clinically significant findings or difference between study arms for both clinical studies.

Serum concentrations of total and free Immunoglobulin E:

For Study CT-P39 3.1, the overall profile of both total IgE and free IgE concentrations were generally similar between the CT-P39 groups and the corresponding Xolair groups.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

The safety profile for omalizumab in special populations has previously been described for the EU originator product Xolair. It does not have to be established again for this biosimilar product if similarity can be shown in a relevant study population.

Nonetheless, to determine the effect of CT-P39 on adolescent and elderly patients in terms of safety, the applicant assessed TEAEs by 12 to 17 years old, 18 to 64 years old and ≥ 65 years old subgroups. A summary of safety during the Overall Period of Study CT-P39 3.1 by age is presented below:

Table 54: Summary of safety by age for patients in study CT-P39 3.1 (Overall Period): Safety Set and Safety-TP2 Subset

	CT-P39 300 mg			Xolair 300 mg			Xolair/CT-P39[1]			Xolair/Xolair[1]			CT-P39 150 mg			Xolair 150 mg		
	12 to 17 (N=2)	18 to 64 (N=190)	≥65 (N=11)	12 to 17 (N=4)	18 to 64 (N=190)	≥65 (N=11)	12 to 17 (N=1)	18 to 64 (N=90)	≥65 (N=5)	12 to 17 (N=3)	18 to 64 (N=88)	≥65 (N=5)	12 to 17 (N=4)	18 to 64 (N=93)	≥65 (N=10)	12 to 17 (N=2)	18 to 64 (N=95)	≥65 (N=6)
	Number (%) of Patients with at Least 1 Event																	
TEAE	1 (50.0)	86 (45.3)	2 (18.2)	2 (50.0)	90 (47.4)	7 (63.6)	0	44 (48.9)	4 (80.0)	2 (66.7)	42 (47.7)	3 (60.0)	2 (50.0)	45 (48.4)	6 (60.0)	1 (50.0)	47 (49.5)	2 (33.3)
Related TEAE	1 (50.0)	16 (8.4)	0	0	20 (10.5)	2 (18.2)	0	11 (12.2)	1 (20.0)	0	8 (9.1)	1 (20.0)	1 (25.0)	5 (5.4)	1 (10.0)	1 (50.0)	12 (12.6)	1 (16.7)
Grade 3 or higher TEAE	0	11 (5.8)	0	0	8 (4.2)	1 (9.1)	0	5 (5.6)	1 (20.0)	0	2 (2.3)	0	0	7 (7.5)	0	0	6 (6.3)	0
TESAE	0	9 (4.7)	0	0	6 (3.2)	0	0	3 (3.3)	0	0	2 (2.3)	0	0	4 (4.3)	0	0	3 (3.2)	0
TEAE leading to study drug discontinuation	0	4 (2.1)	0	0	2 (1.1)	0	0	0	0	0	0	0	0	0	0	0	0	0
TEAE of allergic reaction type I/anaphylaxis	0	0	0	0	1 (0.5)	0	0	0	0	0	0	0	0	0	0	0	0	0
TEAE of injection site reaction	0	5 (2.6)	0	0	11 (5.8)	1 (9.1)	0	5 (5.6)	1 (20.0)	0	5 (5.7)	0	0	2 (2.2)	0	1 (50.0)	2 (2.1)	0
TEAE of allergic reaction type III	0	2 (1.1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Note: Events reported from the CT-P39 300 mg, Xolair 300 mg, CT-P39 150 mg and Xolair 150 mg groups are summarized using the Safety Set and the Xolair/CT-P39 and Xolair/Xolair groups are summarized using the Safety-TP2 Subset.
At each level of summarization, patients are counted once if they reported one or more events.
Parasitic (helminth) infection is not included in the table as none were reported in Study CT-P39 3.1.
[1] Based on patients who were randomized to Xolair for TP1 then re-randomized to CT-P39 or Xolair prior to TP2. The number of patients may not add up to overall numbers in the Xolair 300 mg group due to discontinuation prior to TP2.
Abbreviations: TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

The applicant conducted subgroup analysis of safety data generated from Study CT-P39 3.1 (up to Week 40) in CSU patients by age (12 to 17 years; 18 to 64 years; ≥65 years). The tabulated data, presented above, provides an overview of the number of patients enrolled within each age subgroup. The results of these subgroup analyses did not reveal any specific safety concerns for CT-P39 in relation to specific age, gender, and race subgroups. As the number of patients in the 12 to 17 years and ≥65 years is so low, no robust conclusions can be drawn from the data.

2.6.8.7. Immunological events

Clinical Immunogenicity Results

Immunogenicity was evaluated based on the Safety Set defined as all randomly assigned subjects who received at least 1 dose (full or partial) of either study drug for both CT-P39 clinical studies.

The subjects were considered as post-treatment ADA and NAb positive if they had at least 1 "Positive" ADA and NAb result after drug exposure. Post-treatment ADA and NAb status was determined regardless of the results at pre-dose. The immunogenicity sample at baseline was taken prior to the first administration, so the results at baseline were excluded in order to analyse post-treatment ADA and NAb status.

Study CT-P39 1.1 ADA and NAb formation: Healthy Subjects

In Part 1, 1 (6.7%) subject in CT-P39 treatment group had ADA positive response (ADA titre value of 25) on Day 127 (EOS) and NAb result was negative.

In Part 2, the proportions of subjects who had ADA and NAb positive results up to Day 127 and the proportion of subjects who had post-treatment ADA and NAb positive results are summarised below, followed by ADA titre results.

Table 55: Frequency of Positive ADA and NAb in study CT-P39 1.1 Part 2: Safety Set

Visit	CT-P39 (N=47)	EU-approved Xolair (N=49)	US-licensed Xolair (N=50)
	n (%)		
Day 1 (Pre-dose)			
ADA Positive	3 (6.4%)	3 (6.1%)	1 (2.0%)
NAb Positive (as % of ADA positive)	0	0	0
Day 15			
ADA Positive	0	6 (12.2%)	7 (14.0%)
NAb Positive (as % of ADA positive)	0	1 (16.7%)	3 (42.9%)
Day 43			
ADA Positive	0	5 (10.2%)	6 (12.0%)
NAb Positive (as % of ADA positive)	0	0	0
Day 85			
ADA Positive	0	6 (12.2%)	8 (16.0%)
NAb Positive (as % of ADA positive)	0	0	0
Day 127 (EOS)			
ADA Positive	1 (2.1%)	3 (6.1%)	2 (4.0%)
NAb Positive (as % of ADA positive)	0	0	0
Post-treatment (Up to Day 127)			
ADA Positive	1 (2.1%)	13 (26.5%)	18 (36.0%)
NAb Positive (as % of ADA positive)	0	1 (7.7%)	3 (16.7%)

[redacted]

Note: The proportion of ADA positive subjects was calculated using the number of subjects in the Safety Set. The proportion of NAb positive subjects was re-calculated using ADA positive subjects as a denominator.
Abbreviations: n, number of subjects with the event; N, number of subjects in the Safety Set

Table 56: Summary of ADA Titer Results in Study CT-P39 1.1 Part 2: Safety Set

Visit / Statistic		CT-P39 (N=47)	EU-approved Xolair (N=49)	US-licensed Xolair (N=50)
Day 1 (predose)	n	3	3	1
	Mean (SD)	33.3 (14.43)	33.3 (14.43)	400.0 (N/A)
	Median (Min, Max)	25.0 (25, 50)	25.0 (25, 50)	400.0 (400, 400)
Day 15	n	0	6	7
	Mean (SD)	N/A	29.2 (10.21)	39.3 (28.35)
	Median (Min, Max)	N/A	25.0 (25, 50)	25.0 (25, 100)
Day 43	n	0	5	6
	Mean (SD)	N/A	25.0 (0.00)	29.2 (10.21)
	Median (Min, Max)	N/A	25.0 (25, 25)	25.0 (25, 50)
Day 85	n	0	6	8
	Mean (SD)	N/A	25.0 (0.00)	34.4 (26.52)
	Median (Min, Max)	N/A	25.0 (25, 25)	25.0 (25, 100)
Day 127 (EOS)	n	1	3	2
	Mean (SD)	25.0 (N/A)	25.0 (0.00)	25.0 (0.00)
	Median (Min, Max)	25.0 (25, 25)	25.0 (25, 25)	25.0 (25, 25)

[redacted]

Abbreviations: EOS, End-of-study; Min, Minimum; Max, Maximum; n, The number of patients with the event; N/A, Not applicable; N, The number of patients in each treatment group; SD, Standard deviation

The proportion of subjects who had post-treatment ADA positive results was lower in CT-P39 treatment group than EU-approved Xolair: 1 (2.1%) versus 13 (26.5%) patients. Among the subjects who had post-treatment ADA positive results, 1 (7.7%) subject in EU-approved Xolair had post-treatment NAb positive results while NAb was not observed in any of the subjects in the CT-P39 treatment group. As per the applicant, these incidence results should be interpreted with caution as there was no subject

who showed increasing trend in ADA titre after treatment and the majority had transient low ADA titre (25 which was the lowest quantifiable titre).

No immune-related AEs were reported in the subjects with ADA positive results, except 1 subject (in US-licensed Xolair treatment group) reported Grade 2 urticarial rash that was considered related to the study drug.

Study CT-P39 3 .1 ADA and NAb formation: CSU Patients

The proportions of patients who had ADA and NAb positive results through Week 40 (EOS) and the proportion of patients who had post-treatment ADA and NAb positive results are summarised for TP1 and TP2 and Follow-Up Periods respectively, below.

Table 57: Frequency of ADA and NAb during Treatment Period I up to Week 12 in Study CT-P39 3.1: Safety Set

Visit	CT-P39 300 mg (N=203)	Xolair 300 mg (N=205)	CT-P39 150 mg (N=107)	Xolair 150 mg (N=103)
	n (%)			
Week 0 (Pre-dose)				
ADA Positive	3 (1.5%)	1 (0.5%)	1 (0.9%)	0
NAb Positive (as % of ADA positive)	2 (66.7%)	0	0	0
Week 4 (Pre-dose)				
ADA Positive	2 (1.0%)	2 (1.0%)	0	0
NAb Positive (as % of ADA positive)	0	1 (50.0%)	0	0
Week 8 (Pre-dose)				
ADA Positive	0	3 (1.5%)	0	0
NAb Positive (as % of ADA positive)	0	1 (33.3%)	0	0
Week 12 (Pre-dose)				
ADA Positive	1 (0.5%)	0	2 (1.9%)	0
NAb Positive (as % of ADA positive)	1 (100.0%)	0	1 (50.0%)	0

Note: The proportion of ADA positive patients was calculated using the number of patients in the Safety Set. The proportion of NAb positive patients was re-calculated using ADA positive patients as a denominator.
Abbreviations: ADA, anti-drug antibody; N, total number of patients; n, number of patients with the event; NAb, neutralizing antibody

Table 58: Frequency of ADA and NAb during Treatment Period II and Follow-up Period in Study CT-P39 3.1: Safety-TP2 Subset

Visit	CT-P39/ CT-P39 (N=187)	Xolair/ CT-P39 (N=96)	Xolair/ Xolair (N=96)	CT-P39 150/300 (N=101)	Xolair 150/300 (N=98)
	n (%)				
Week 16 (Pre-dose)					
ADA Positive	2 (1.1%)	1 (1.0%)	0	3 (3.0%)	0
NAb Positive (as % of ADA positive)	1 (50.0%)	0	0	3 (100.0%)	0
Week 20 (Pre-dose)					
ADA Positive	5 (2.7%)	0	1 (1.0%)	4 (4.0%)	1 (1.0%)
NAb Positive (as % of ADA positive)	4 (80.0%)	0	0	4 (100.0%)	1 (100.0%)
Week 24/EOT					

ADA Positive	9 (4.8%)	2 (2.1%)	0	4 (4.0%)	1 (1.0%)
NAb Positive (as % of ADA positive)	2 (22.2%)	0	0	3 (75.0%)	1 (100.0%)
Week 40/EOS					
ADA Positive	14 (7.5%)	3 (3.1%)	0	7 (6.9%)	2 (2.0%)
NAb Positive (as % of ADA positive)	7 (50.0%)	1 (33.3%)	0	6 (85.7%)	2 (100.0%)

Note: The proportion of ADA positive patients was calculated using the number of patients in the Safety-TP2 Subset. The proportion of NAb positive patients was re-calculated using ADA positive patients as a denominator.
Abbreviations: ADA, anti-drug antibody; EOS, end-of-study; EOT, end-of-treatment; N, total number of patients; n, number of patients with the event; NAb, neutralizing antibody

The ADA titers are summarised for TP1 and TP2 and Follow-Up Periods below, with ADA titers presented in a scatter plot figure below.

Table 59: Summary of ADA Titer Results during Treatment Period I up to Week 12 in Study CT-P39 3.1: Safety Set

Visit / Statistic		CT-P39 300 mg (N=203)	Xolair 300 mg (N=205)	CT-P39 150 mg (N=107)	Xolair 150 mg (N=103)
Week 0	n	3	1	1	0
	Mean (SD)	275.0 (216.5)	400.0 (N/A)	25.0 (N/A)	N/A
	Median (Min, Max)	400.0 (25, 400)	400.0 (400, 400)	25.0 (25, 25)	N/A
Week 4	n	2	2	0	0
	Mean (SD)	25.0 (0.0)	75.0 (35.4)	N/A	N/A
	Median (Min, Max)	25.0 (25, 25)	75.0 (50, 100)	N/A	N/A
Week 8	n	0	3	0	0
	Mean (SD)	N/A	158.3 (209.7)	N/A	N/A
	Median (Min, Max)	N/A	50.0 (25, 400)	N/A	N/A
Week 12	n	1	0	2	0
	Mean (SD)	25.0 (N/A)	N/A	37.5 (17.7)	N/A
	Median (Min, Max)	25.0 (25, 25)	N/A	37.5 (25, 50)	N/A

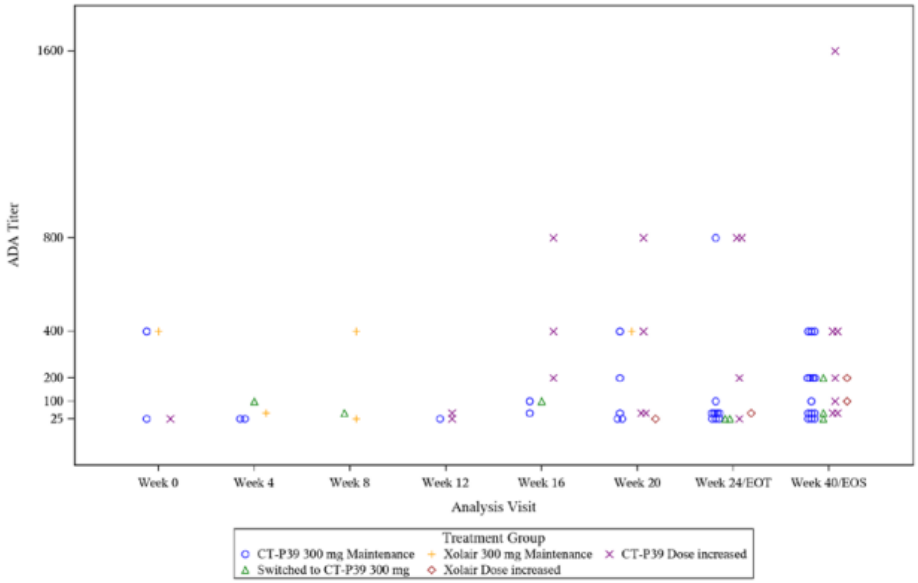
Abbreviations: Min, Minimum; Max, Maximum; n, The number of patients with the event; N/A, Not applicable; N, The number of patients in each treatment group; SD, Standard deviation

Table 60: Summary of ADA Titer Results during Treatment Period II and follow-up in Study CT-P39 3.1: Safety-TP2 Subset

Visit / Statistic		CT-P39/ CT-P39 (N=187)	Xolair/ CT-P39 (N=96)	Xolair/ Xolair (N=96)	CT-P39 150/300 (N=101)	Xolair 150/300 (N=98)
Week 16	n	2	1	0	3	0
	Mean (SD)	75.0 (35.4)	100.0 (N/A)	N/A	466.7 (305.5)	N/A
	Median (Min, Max)	75.0 (50, 100)	100.0 (100, 100)	N/A	400.0 (200, 800)	N/A
Week 20	n	5	0	1	4	1
	Mean (SD)	140.0 (162.6)	N/A	400.0 (N/A)	325.0 (357.1)	25.0 (N/A)
	Median (Min, Max)	50.0 (25, 400)	N/A	400.0 (400, 400)	225.0 (50, 800)	25.0 (25, 25)
Week 24 (EOT)	n	9	2	0	4	1
	Mean (SD)	130.6 (252.1)	25.0 (0.0)	N/A	456.3 (403.3)	50.0 (N/A)
	Median (Min, Max)	50.0 (25, 800)	25.0 (25, 25)	N/A	500.0 (25, 800)	50.0 (50, 50)
Week 40 (EOS)	n	14	3	0	7	2
	Mean (SD)	166.1 (145.0)	91.7 (94.6)	N/A	400.0 (550.0)	150.0 (70.7)
	Median (Min, Max)	150.0 (25, 400)	50.0 (25, 200)	N/A	200.0 (50, 1600)	150.0 (100, 200)

[redacted]

Abbreviations: EOS, end-of-study; EOT, end-of-treatment; Min, Minimum; Max, Maximum; n, The number of patients with the event; N/A, Not applicable; N, The number of patients in each treatment group; SD, Standard deviation



[redacted]

Figure 12: Scatter Plot of ADA Titer by Treatment Arm in Study CT-P39 3.1: Safety-TP2 Subset

The incidence of ADA and NAb at each timepoint across all groups was generally low (below 5%) through Week 24 (EOT). The proportions of patients who had positive ADA results at Week 40/EOS were 14 (6.9%) patients for Arm 1, 3 (1.5%) patients for Arm 2, (3 [3.1%] patients in Arm 2-1 for the Safety-TP2 Subset), 7 (6.5%) patients in Arm 3, and 2 (1.9%) patients in Arm 4 for the Safety Set. Among them, 7 (3.4%) patients for Arm 1, 1 (0.5%) patient for Arm 2 (1 [1.0%] patient in Arm 2-1 for the Safety-TP2 Subset), 6 (5.6%) patients for Arm 3, and 2 (1.9%) patients for Arm 4 had positive NAb result at Week 40/EOS for the Safety Set.

At Week 40/EOS, the proportions of patients who had positive ADA/NAb results were higher in CT-P39 treatment arms (Arm 1 and Arm 3) compared to Xolair treatment arms (Arm 2-2 and Arm 4) or switched to CT-P39 arm (Arm 2-1).

ADA titre values were generally low throughout the study, with four patients recording titers higher than 800. All were in CT-P39 treatment arms:

- One patient in the CT-P39/CT-P39 treatment group had a titer value of 800 at Week 24.
- One patient in the CT-P39 150/300 treatment group had a titer value of 800 at Week 16 and Week 20.
- One patient in the CT-P39 150/300 treatment group had titer values of 800 and 1600 at Week 24 and Week 40, respectively.
- One patient in the CT-P39 150/300 treatment group had a titer value of 800 at Week 24

For these four patients, ADAs were high at only one or two timepoint, there was no pattern observed for gradual titer increase and none of these patients reported immune-related AEs, ISRs, or hypersensitivity.

ADA incidence and immune-mediated AEs:

In Study CT-P39 3.1, there was one immune-mediated AE reported in a patient after ADA detection. One patient (CT-P39 150/300 treatment group), who was ADA positive at Week 20, Week 24 (EOT) and Week 40 (EOS), reported Grade 1 oral allergy syndrome at EOT (Week 24) visit date. The event was considered to be unrelated to the study drug and the patient recovered from the event. The patient had ongoing medical history of drug hypersensitivity.

Two other immune-mediated AEs were reported in the ADA positive subset; one (grade 1 seasonal allergy) in the Xolair/CT-P39 switching arm (unrelated), and one (grade 2 Type III immune complex mediated reaction) in the CT-P39 maintenance arm (possibly related). Both were reported prior to ADA detection.

There were no newly reported immune-related AEs during the Follow-up Period in patients with ADA positive results during the study.

In Study CT-P39 1.1, among the subjects with ADA positive results at any time during the entire period after the first study drug administration, 3 subjects had immune related AE which were related to the study drug. All of them were from US-approved Xolair treatment group and reported immune-related AEs prior to ADA detection.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Not applicable.

2.6.8.9. Discontinuation due to adverse events

Study CT-P39 1.1: Healthy Subjects

No TEAEs leading to study discontinuation were reported in either part of Study CT-P39 1.1

Study CT-P39 3.1: CSU Patients

In Study CT-P39 3.1, during TP1, TEAEs leading to study drug discontinuation were reported for 3 (1.5%) patients in the CT-P39 300 mg group and 2 (1.0%) patients in the Xolair 300 mg group. These are tabulated by SOC and PT, with severity and assigned relatedness, below:

Table 61: TEAEs leading to study drug discontinuation by SOC and PT in Study CT-P39 3.1 (Treatment Period I): Safety Set

System Organ Class Preferred Term	CT-P39 300 mg (N=203)	Xolair 300 mg (N=205)	CT-P39 150 mg (N=107)	Xolair 150 mg (N=103)
Number (%) of patients with ≥ 1 TEAE leading to study drug discontinuation	**3 (1.5)**	**2 (1.0)**	**0**	**0**
Cardiac disorder	**1 (0.5)**	**0**	**0**	**0**
Myocardial ischaemia - Grade 3, Related	1 (0.5)	0	0	0
General disorders and administration site conditions	**1 (0.5)**	**1 (0.5)**	**0**	**0**
Injection site reaction - Grade 2, Related	0	1 (0.5)	0	0
Oedema peripheral - Grade 3, Related	1 (0.5)	0	0	0
Infections and infestations	**1 (0.5)**	**0**	**0**	**0**
Bronchitis - Grade 2, Unrelated	1 (0.5)	0	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**0**	**1 (0.5)**	**0**	**0**
Papillary thyroid cancer - Grade 3, Unrelated	0	1 (0.5)	0	0

Note: At each level of summarization, patients are counted once if they reported one or more events.
Abbreviations: PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event

The two reported grade 3 related TESAE that lead to study discontinuation (myocardial ischaemia and oedema peripheral) are outlined in Section 2.6.8.3 of this Overview. No TEAE leading to study discontinuation (by SOC or PT) was reported in more than one patient.

During TP2, TEAE leading to study drug discontinuation was reported for 1 (0.5%) patient in the CT-P39/CT-P39 group. The event was a grade 2 TEAE of haemorrhoids, which was considered to be possibly related to the study drug.

2.6.8.10. Post marketing experience

CT-P39 has not been marketed in any regions and there is no post-marketing data available to report.

2.6.9. Discussion on clinical safety

Safety and immunogenicity data on CT-P39 are available from two clinical studies (Study CT-P39 1.1 and Study CT-P39 3.1), where both were assessed as part of the secondary study objectives.

In Study CT-P39 1.1, in total (Part 1 and Part 2), 64 healthy subjects were exposed to a single dose of CT-P39 150 mg.

In Study CT-P39 3.1, a total of 178 CSU patients received all 6 per protocol doses (6 months exposure) of CT-P39 300 mg, with 93 having received all 6 doses of EU-approved Xolair 300 mg. A total of 93, 98 and 93 patients received all 6 doses, as per protocol, in Arms 2-1 (switching), 3 (CT-P39 increasing) and 4 (EU-approved Xolair increasing) respectively.

Study CT-P39 3.1 was ongoing at the time of the initial MAA, and safety and immunogenicity data through Week 24 (EOT) only were provided in an interim Week 24 Clinical Study Report (CSR) at that time. The final CSR with 40-week (EOS) safety and immunogenicity data from the Phase 3 study was submitted at Day 120 during the MAA procedure. In general, the final CSR data are consistent with that already presented in the interim report. Overall, the safety profile remains unchanged and is comparable to the reference Xolair.

Demographic and baseline characteristics

In the safety population of **Study CT-P39 1.1**, the demographic and baseline characteristics were generally balanced between all cohorts in both parts of the study. No clinically relevant differences were observed with respect to subjects' medical history and surgical history, and prior or concomitant medications.

In **Study CT-P39 3.1**, demographic characteristics were similar between the 4 treatment arms of Safety Set (TP1), with no clinically relevant imbalances observed. The characteristics of patients appeared similar when compared to patients recruited in the pivotal Xolair trials, Q4881g and Q4882g.

Demographic characteristics for the Safety-TP2 Subset showed a similar trend with those of the Safety Set (TP1) in all treatment arms. There were no clinically relevant differences in demographic characteristics and stratification details between the 5 treatment arms in TP2.

No notable clinically significant differences between the medical and surgical history, or prior medications in any cohort of either treatment period were observed.

Regarding concomitant medication, in Study CT-P39 3.1, concomitant use of corticosteroids for systemic use was higher in the Overall Period Safety Set in the CT-P39 300 mg (6.9%) arm when compared to Xolair 300 mg (2.4%), CT-P39 150 mg (3.7%) and Xolair 150 mg (3.9%) arms. This was also observed in the Overall Period-TP2 Subset in the CT-P39 300 mg/ 300 mg (5.9%) arm when compared to Xolair 300 mg/ CT-P39 300 mg (0%), Xolair 300 mg/ Xolair 300 mg (3.1%), CT-P39 150 mg/ 300 mg (3%) and Xolair 150 mg/ Xolair 300 mg (3%) arms. The applicant provided adequate justification that concomitant use of systemic corticosteroids did not influence the observed safety profile of the study drugs in Study CT-P39 3.1.

Adverse events

In the principal part of **Study CT-P39 1.1**, Part 2, there was a similar incidence of TEAEs reported: 33 (70.2%) and 37 (75.5%) subjects in the CT-P39 150 mg and EU-approved Xolair 150 mg, respectively.

The most frequently reported TEAE by SOC, for at least 5% of subjects in either group, was nervous system disorders (headache by PT) with similar incidence observed between the two cohorts. This was followed by general disorders and administration site conditions, by PT, injection site reactions. A higher incidence was reported for the TEAEs nausea (12.8% versus 4.1%) and injection site reaction (17% versus 10.2%) in the CT-P39 group when compared to the EU-approved Xolair group. However, it is likely that the small sample size in these groups might have contributed to the observed imbalance.

The majority of TEAEs were grade 1 or grade 2 in intensity, and grade 3 TEAEs were reported for one subject in each group. Both were considered unrelated to the study drug.

The most frequently reported related TEAE by SOC was nervous system disorders, with headache being the most common by PT. The only reported TEAESIs were those of injection site reaction, with incidence given above. Only one SAE was reported in the CT-P39 arm, but this was considered unrelated to the study drug.

In part 1 of Study CT-P39 1.1, TEAEs were reported for 6 (40.0%) and 9 (60.0%) subjects in the CT-P39 and EU-approved Xolair groups, respectively. There were no notable differences between TEAEs reported in terms of their type, incidence, severity, or relatedness. There were no SAEs. TEASIs reported were injection site reactions, with a similar incidence between both arms.

Overall, none of the treatment-related TEAEs reported in Part 1 and Part 2 of Study CT-P39 1.1 were unexpected and the reported safety findings after a single dose in the PK study (both Parts) in healthy subjects reflect the known safety profile of the originator as per Xolair's SmPC.

Study CT-P39 3.1 final CSR provided full safety data from TP1 (Safety Set), TP2 (Safety-TP2 Subset), the Follow-Up Period, and Overall Period (Week 0 through Week 40).

During the Overall Period, TEAEs were reported for 89 (43.8%) patients in the CT-P39 300 mg group, 99 (48.3%) patients in the Xolair 300 mg group, 48 (50.0%) patients in the Xolair/CT-P39 group and 47 (49.0%) patients in the Xolair/Xolair group.

The most frequently reported TEAE by SOC was infections and infestations (23.6%, 27.3%, 27.1% and 29.2%) patients in the CT-P39 300 mg, Xolair 300 mg, Xolair/CT-P39 and Xolair/Xolair groups, respectively) and by PT was COVID-19 (5.9%, 8.8%, 9.4% and 9.4%, respectively), followed by PT nasopharyngitis (5.4%, 6.8%, 5.2%, 8.3%, respectively).

During the Overall Period of Study CT-P39 3.1, related TEAEs were reported for 17 (8.4%), 22 (10.7%), 12 (12.5%) and 9 (9.4%) patients in the CT-P39 300 mg, Xolair 300 mg, Xolair/CT-P39 and Xolair/Xolair groups, respectively. The most frequently reported related TEAE by SOC was general disorders and administration site conditions (3.4%, 6.8%, 9.4% and 4.2%, respectively) and by PT was injection site reaction (2.0%, 5.4%, 6.3% and 4.2%, respectively).

The majority of TEAEs during the Overall Period were grade 1 or grade 2 in intensity. Of note, a higher proportion of patients from the CT-P39/CT-P39 group (Arm 1) in TP2 were reported as having a grade 3 or higher TEAEs. This was most likely due to chance finding as all events were considered unrelated to the study drug and were of a different type.

There was one death (completed suicide) reported in a CSU patient in Arm 1 (CT-P39 300 mg/CT-P39 300 mg) of TP2 in the phase 3 study. The event was considered by the investigator to be unrelated to the study drug. The CHMP considered the investigator's conclusion acceptable.

During the Overall Period of Study CT-P39 3.1, TESAEs were reported for 9 (4.4%) patients in the CT-P39 300 mg group, 6 (2.9%) patients in the Xolair 300 mg group, 3 (3.1%) patients in the Xolair/CT-P39 group and 2 (2.1%) patients in the Xolair/Xolair group. There were no TESAEs by PT that were reported for more than 1 patient within any of the CT-P39 300 mg, Xolair 300 mg, Xolair/CT-P39 and Xolair/Xolair groups during TP1 and TP2. Of these events, only grade 3 TESAEs of myocardial ischaemia and oedema peripheral and grade 2 TESAE of arthropathy reported in the CT-P39 300 mg group were considered possibly related to the study drug.

In the reported TESAE of myocardial ischaemia, in a 53-year-old male patient, no prior diagnosis of acute coronary syndrome or ischemic heart disease had been made. Of note, in line with the RMP for Xolair, the applicant has proposed inclusion of Arterial Thromboembolic Events (ATEs) as an important potential risk. As per Xolair's SmPC, ATEs are highlighted in section 4.8, not as an ADR, but as a summary of the available data from the pooled CT database and observational study.

In the reported TESAE of oedema peripheral, the investigator assessed the event as possibly related to the study drug since temporal relationship could not be ruled out, but overlapping confounding factors were identified (starting hormonal contraception for the first time, COVID-19 vaccination and risk factors of obesity, and history of smoking).

During the Overall Period of Study CT-P39 3.1, TEAEs leading to study drug discontinuation were reported for 4 (2.0%) patients in the CT-P39 300 mg and 2 (1.0%) patients in the Xolair 300 mg group. There were no TEAEs by PT leading to study drug discontinuation that were reported for more than 1 patient within both treatment groups. Out of these events, grade 3 TESAEs of myocardial ischaemia and oedema peripheral and grade 2 TEAE of haemorrhoids reported in the CT-P39 300 mg group were considered to be possibly related to the study drug and grade 2 TEAE of injection site reaction reported in the Xolair 300 mg group was considered to be definitely related to the study drug.

In terms of reported TEAESI, a higher incidence of inject site reactions was observed in the Xolair study arms in the phase 3 study. During the Overall Period, TEAEs of injection site reaction were reported for 2.5% patients in the CT-P39 300 mg group, 5.9% patients in the Xolair 300 mg group, 6.3% patients in the Xolair/CT-P39 group, 5.2% patients in the Xolair/Xolair group, 1.9% patients in the CT-P39 150 mg group and 2.9% patients in the Xolair 150 mg group.

Of note, a difference in trends in the occurrence of injection site reactions was observed between Studies CT-P39 1.1 and CT-P39 3.1. In the PK study, there was a higher incidence of injection site reactions in the CT-P39 arm versus the EU-approved Xolair arm (17% v 10.2%). The opposite trend was observed in the phase 3 study, with a higher incidence being reported in the Xolair arms when compared to the CT-P39 arms. In response to a request to discuss these observations, the applicant concluded that the numerical difference between the studies in terms of incidence of ISR between groups was likely by chance, due to the variations from the small sample sizes, and not indicative of an actual trend in ISR incidence between groups. This justification is accepted.

In relation to TEAEs reported in the increasing dose arms (Arm 3 [CT-P39 150 mg/ 300 mg] and Arm 4 [Xolair 150 mg/300 mg]) and the switching arm (Arm 2-1 [Xolair 300 mg/CT-P39 300 mg]) of Study

CT-P39 3.1, the proportion of patients with at least 1 TEAE was comparable between all treatment groups, regardless of the study drug, dosage, switching treatment or increasing dosage. No notable differences in the safety profile of the increasing dose or switching arms were observed.

Concluding on the complete safety data from health subjects in Study CT-P39 1.1 and CSU patients from Study CT-P39 3.1, CT-P39 and Xolair have been shown to have comparable safety profiles in terms of type, frequency, severity, and relatedness of TEAEs. Data presented are consistent with the known safety profile of Xolair, and no new safety concerns have been identified.

Immunogenicity

Immunogenicity was a secondary objective in both studies CT-P39 1.1 and CT-P39 3.1 and was assessed by means of monitoring development of ADAs and NAbs during the studies.

In Part 2 of **Study CT-P39 1.1**, the incidence of post-treatment ADA was lower in the CT-P39 group (n=1, 2.1%) than the EU-approved Xolair group (n=13, 26.5%). NAb was not detected in the CT-P39 group and was detected in 1 subject in the EU-approved Xolair group. There was no subject with an increasing trend in ADA titre after treatment, and the majority had low ADA titre values.

In Study **CT-P39 3.1** in CSU patients, the incidence of post-treatment ADA was generally low at all timepoints and across all treatment groups during Treatment Period I. Titer values were generally low. The incidence of NAb positive results in patients with detected ADAs was variable between treatment arms and at each timepoint.

During Treatment Period II and the Follow-Up Period, although the number of patients with positive ADA results was low, an increased incidence of ADA positive patients was observed in the CT-P39 300mg /CT-P39 300mg treatment arm over time, from Week 16 (1.1%), Week 20 (2.7%), Week 24 (4.8%) to Week 40 (7.5%). An increase in incidence was also observed in the CT-P39 150 mg/ CT-P39 300 mg arm from Week 16. Additionally, it was noted that, although ADA titers were generally low, 4 high titers (≥ 800) were recorded in CT-P39 arms (only), and at later timepoints in TP2 (from Week 20).

Between **Studies CT-P39 1.1 and 3.1**, a different pattern in ADA positivity was also observed, i.e., a lower number of positive ADA subjects treated with CT-P39 compared to Xolair in the PK study versus a higher number of ADA positive patients in the CT-P39 arm compared to Xolair or Xolair/CT-P39 during TP2 in the Phase 3 study.

The applicant was requested to provide reasons for the above observations and discuss the possible clinical consequences of same. A root cause analysis concluded that there is no expected difference in immunogenicity between CT-P39 and EU-approved Xolair based on analytical similarity studies, subject/patient level factors, and operational aspects of IP and immunogenicity sample handling. The increased sensitivity of the assay method used in both CT-P39 clinical studies when compared to that of historical assay methods may have led to the increased detection of ADA positives at titers which have no or minimal impact on PK/PD, efficacy, and safety, but result in higher rates of ADA reporting. This was accepted by the CHMP.

As per EMEA/CHMP/BMWP/42832/2005 Rev1, for medicinal products with chronic treatment indications, immunogenicity data for one year of treatment should normally be available pre-authorisation but shorter follow up is possible with a proper justification. Submission of the final CSR for Study CT-P39 3.1 has provided immunogenicity data for a 6-month exposure period and subsequent 16-week Follow-Up Period. The applicant was requested to justify the adequacy of the immunogenicity database in demonstrating comparability of immunogenicity profiles between CT-P39 and Xolair in light of trends observed in the on-treatment population.

In response, the applicant highlighted the recognised low immunogenic potential and characterised safety profile of the originator with respect to reported immediate and delayed immune-mediated adverse reactions, and that historical data do not indicate that there are clinically relevant

consequences of ADAs to omalizumab with respect to the occurrence of immune-mediated reactions. This is supported by Study CT-P39 3.1 data.

Furthermore, known immune-mediated AEs occur within 6 months (e.g., injection site reactions) or are rare and therefore are unlikely to be detected in a 6 month or 1 year study (e.g., anaphylactic reactions). Most of the relevant AEs described for Xolair would have been well-captured timewise in the studies due to their early occurrence, and all described safety events including immune-related AEs are clinically well manageable and described in proposed product information. In addition, there were no cases of anaphylaxis reported in Studies CT-P39 1.1 and CT-P39 3.1, and no adverse safety profile, including immune-related events, was observed. Anaphylaxis/anaphylactoid reactions will continue to be monitored in the post-marketing risk management plan.

Overall, the applicant's justification that the submitted immunogenicity database is adequate in determining whether or not the immunogenicity response of CT-P39 and Xolair is similar is accepted. Although differing trends in ADA status were observed in both clinical studies, differences in immunogenicity did not correlate to clinically significant differences in safety and efficacy outcomes between CT-P39 and Xolair.

2.6.10. Conclusions on the clinical safety

Overall, the CT-P39 clinical development programme and design of the studies is considered adequate to evaluate the comparability of CT-P39 and its reference product EU-approved Xolair in terms of safety and immunogenicity. Completed datasets from both the single-dose, Phase 1, PK study in healthy subjects (Study CT-P39 1.1) and the repeat-dose, Phase 3, therapeutic equivalence, study in CSU patients (Study CT-P39 3.1) have been submitted.

On the basis of safety data presented, the safety profile of CT-P39 and EU-approved Xolair is considered similar. TEAEs were generally low across all treatment groups in both studies. No notable imbalances were observed with respect to type, severity, or relatedness of reported TEAEs between treatment groups in either study. No emerging safety signals were reported, and data were generally in line with the known safety profile of the reference product Xolair.

On the basis of immunogenicity data submitted in healthy subjects and CSU patients, despite differing trends in ADA detection between studies and between treatment periods in the Phase 3 study, there were no notable clinically significant differences in the overall safety profile of CT-P39 and Xolair observed when evaluated according to ADA status.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	• Anaphylaxis/anaphylactoid reactions • Churg Strauss Syndrome (CSS)/Hypereosinophilic Syndrome (HES)
Important potential risks	• Arterial Thromboembolic Events (ATEs) • Malignant neoplasms in adults and adolescents ≥12 years of age • Malignant neoplasms (children 6 to less than 12 years old)
Missing information	None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Anaphylaxis/anaphylactoid reactions (Important identified risk)	Routine risk minimisation measures: • *SmPC section 4.3 and 4.8* • *SmPC sections 4.2 and 4.4 where recommendations for monitoring and managing anaphylaxis, training, and selecting appropriate patient for home use to lower the risk for anaphylaxis are included.* • *PL sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire. Additional pharmacovigilance activities: None
Churg Strauss Syndrome (CSS) / Hypereosinophilic Syndrome (HES) (Important identified risk)	Routine risk minimisation measures: • *SmPC section 4.8* • *SmPC section 4.4 where guidance for physicians is given to monitor sign and symptoms related to CSS and HES, and how to manage this risk.* • *PL sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Arterial Thromboembolic Events (ATEs) (Important potential risk)	Routine risk minimisation measures: • *SmPC section 4.8* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire. Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Malignant neoplasms in adults and adolescents ≥ 12 years of age (Important potential risk)	Routine risk minimisation measures: *None* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire. Additional pharmacovigilance activities: None
Malignant neoplasms (children 6 to less than 12 years old) (Important potential risk)	Routine risk minimisation measures: *None* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire. Additional pharmacovigilance activities: None

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the

basis of a double bridging report making reference to the parent PL of Xolair 75 mg solution for injection in pre-filled syringe/ Xolair 150 mg solution for injection in pre-filled syringe (EMEA/H/C/000606/X/0115/G) for the purpose of content (including key safety messages) and to the parent PL of Remsima 120 mg solution for injection in pre-filled syringe (EMEA/H/C/002576/X/0062) for the purpose of design, layout and format. Xolair 75 mg and 150 mg PL and Remsima 120 mg PL have successfully undergone full user testing. This approach is accepted. Differences in content and design/layout/format of the daughter PL to parent PLs have been provided and sufficiently addressed. The proposed bridging is considered acceptable as parent and daughter PLs are sufficiently similar in both content and layout.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Omlyclo (omalizumab) is included in the additional monitoring list as it is a biological product.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Celltrion has developed Omlyclo (CT-P39, omalizumab) as a proposed biosimilar product to Xolair (omalizumab), which was first authorised via the Centralised Procedure in the EU on 25-10-2005 (marketing authorisation holder Novartis Europharm Limited). Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody is an IgG1 kappa that contains human framework regions with the complementary-determining regions of a murine parent antibody that binds to IgE.

Xolair is available in 4 presentations: 75 mg and 150 mg, powder and solvent for solution for injection, or 75 mg and 150 mg solution for injection in pre-filled syringe. CT-P39 drug product is presented in syringes (with safety needle guard, PFS-S) containing 75 mg or 150 mg omalizumab, as are EU-approved Xolair 75 mg and 150 mg drug products. In the present MAA only the 75 mg and 150 mg, solution for injection in pre-filled syringe presentations are applied for.

Celltrion is seeking approval for CT-P39 for the same indications approved for the reference medicinal product Xolair:

- Allergic asthma in adults, adolescents (12 years and above) and children (6 to <12 years of age)
- Chronic rhinosinusitis with nasal polyps in adults (18 years and above)
- Chronic spontaneous urticaria in adult and adolescent (12 years and above)

Quality aspects

Analytical similarity of CT-P39 was assessed in a comprehensive similarity exercise using EU-sourced Xolair as reference medicinal product (RMP). The comparability assessment was, for the most part, conducted as per the relevant EU guidelines on the development of similar biological medicinal

products (CHMP/437/04 Rev 1, EMA/CHMP/BWP/247713/2012), as well as the principles of comparability as per ICH Q5E.

The 2-way analysis included batches of EU-approved Xolair, and batches of CT-P39. The similarity ranges were established using data from analysis of EU-approved Xolair batches. The approaches to compare physicochemical characteristics and biological quality attributes were described. The Applicant provided graphical plots and summary tables of the individual analytical results, which allow for ease of assessment regardless of the defined quality ranges. The data is clearly presented and no concerns were raised regarding the approaches used.

Clinical aspects

The clinical development programme for CT-P39 comprises of two comparative studies with the aim of establishing PK and therapeutic similarity to the reference product EU-approved Xolair: one comparative PK study conducted in healthy subjects (Study CT-P39 1.1) and one comparative efficacy, safety, immunogenicity, and PK study in patients with CSU (Study CT-P39 3.1).

Study CT-P39 1.1 (pivotal pharmacokinetics [PK] study) is a Phase 1, randomised, 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.

Study CT-P39 3.1 (comparative efficacy and safety study): a double-blind, randomised, active-controlled, parallel group, Phase 3 study to compare efficacy and safety of CT-P39 and Xolair in patients with CSU who remain symptomatic despite H1-antihistamine treatment.

In study CT-P39 1.1, the primary objective was to demonstrate PK similarity of CT-P39 to both EU-approved Xolair and US-licensed Xolair, and to demonstrate similarity between EU-approved Xolair and US-licensed Xolair, in terms of the primary PK endpoints of C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$. For this EU MAA, the similarity assessment will focus on the PK similarity between CT-P39 and EU-approved Xolair. The selected endpoints are in line with relevant EMA guideline (EMA/CHMP/BMWP/403543/2010) for a single dose study with subcutaneous administration. The assessment of biosimilarity was based on 90% confidence intervals (CIs) for the ratio of the geometric means (CT-P39/EU-approved Xolair) for Cmax, AUC0-last, and AUC0-inf of the omalizumab concentrations, which had to be contained within the acceptance limits of 80-125%. The equivalence margins used in the study are in line with conventionally used margins for biosimilar products. Secondary objectives comprised additional PK parameters to support similarity comparability (t_{max}, Kel, t1/2, Vz/F, CL/F, $\%AUC_{ext}$, λz), PD parameters (total and free IgE), comparison of safety, tolerability and immunogenicity between CT-P39 and reference products.

In study CT-P39 3.1, the primary objective was to evaluate the therapeutic similarity of CT-P39 to EU-approved Xolair in terms of efficacy in patients with CSU. The primary efficacy endpoint was the change from baseline in ISS7 of 300 mg of CT-P39 (Arm 1) and 300 mg of Xolair (Arm 2) at Week 12. Secondary Objectives were to compare efficacy of CT-P39 and EU-approved Xolair by measuring additional efficacy endpoints commonly used in patients with CSU, to compare the safety, tolerability, and immunogenicity of CT-P39 and EU-approved Xolair, and to compare secondary PK by measuring C_{trough} of CT-P39 and EU-approved Xolair.

3.2. Results supporting biosimilarity

Quality aspect

In general, the quality attributes analysed were shown to be highly similar between CT-P39 and EU-approved Xolair. A large panel of relevant methods has been used to characterise and compare the

most relevant physicochemical and biological quality attributes of the omalizumab molecule.

Overall, the comparative analytical assessment demonstrated that the primary and higher order structure, functional binding, and bioactivity of CT-P39 is highly comparable to EU-approved Xolair. For C-terminal lysine variants, charge, and purity/impurities, some minor differences were observed. However, any differences identified were considered minor and were in general sufficiently justified by the applicant, hence do not impact on the biosimilarity claim. Additional characterisation of the product-related variants and impurities, impact of aglycosylation, and additional MoA studies were performed to support the applicant's conclusion that any differences observed in the comparative assessment have no significant impact on biological activities and therefore have no clinically meaningful impact. A forced degradation study was also performed, and the results show that the rates and levels of degradants were similar between the two products.

Clinical Aspects

Pharmacokinetics

In the pivotal phase 1 PK study (CT-P39 1.1) the primary PK endpoints were $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max}. PK comparability has been demonstrated according to the pre-specified acceptance criteria; the GMRs and 90% CIs were within the 80-125% acceptance criteria for the primary PK endpoints of $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, and Cmax. The GMRs and 90% CIs for $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$ and C_{max} are acceptable.

In the phase 3 study (CT-P39 3.1) a secondary objective was to compare the pharmacokinetics of CT-P39 with EU-approved Xolair by measuring C_{trough}. Overall, the C_{trough} values were comparable between CT-P39 and the corresponding EU-approved Xolair groups for all timepoints during Treatment Period I and Treatment Period II.

Pharmacodynamics

In study CT-P39 1.1 pharmacodynamics of CT-P39 and EU-approved Xolair were assessed by measuring free IgE and total IgE as secondary outcomes to the study in healthy subjects. CT-P39 1.1 showed that the pharmacodynamic parameters for free IgE and total IgE in healthy subjects were overall similar.

In Study CT-P39 3.1 the total IgE and free IgE were measured in patients with CSU as a safety endpoint. CT-P39 3.1 showed that the mean total IgE was increased and mean free IgE was suppressed in both the CT-P39 arms and the EU-approved Xolair arms similarly.

Efficacy

In the efficacy and safety study CT-P39 3.1, CT-P39 demonstrated similar efficacy as EU-approved Xolair in primary and secondary efficacy endpoints.

The primary endpoint, change from Baseline in Weekly Itch Severity Score at week 12 was met. Although a slightly better response and therefore lower ISS7 score was reported in patients receiving treatment with 300 mg Xolair (at week 12 a change from baseline in ISS7 was - 9.98 in this group) as compared to those treated with 300 mg CT-P39 (at week 12 ISS7 was -9.21), the 95% CI of treatment difference in the mean was [-0.37, 1.90] which was within the predefined equivalence margin of [-2.0, 2.0].

The primary endpoint results for the mITT population were consistent with those reported for the PP Set. In the PP set, the 95% CI of treatment difference in the mean change from baseline in ISS7 at Week 12 between 300 mg of CT-P39 and 300 mg of Xolair was [-0.45, 1.84]

The result of multiple imputation and tipping point analysis showed that missing data had no major impact on the result for the primary efficacy endpoint.

In relation to the mean change from baseline in weekly ISS (ISS7), weekly HSS (HSS7), and weekly UAS (UAS7), results at each timepoint were similar between patients receiving 300 mg of CT-P39 (Arm

1) and those on 300 mg of Xolair (Arm 2). For these endpoints, the 95% confidence interval (CI) of the difference contained zero.

For endpoints investigating percentage of responders, similar results were reported. For all these endpoints, except those collected at week 8, 95% CI of the difference contained zero. At week 12, these differences became non-significant.

Safety

In the phase 1 PK study (Part 2) in healthy subjects, there was a similar incidence of TEAEs reported in CT-P39 and EU-approved Xolair arms, with a higher incidence being reported in the EU-approved Xolair arm for TEAEs considered related to the study drug. The majority of TEAEs were grade 1 or grade 2 in severity. There were no deaths reported, and there was one TESAE observed in the CT-P39 which was considered unrelated to the study drug. The only reported type of TEAESI were those of injection site reaction (all grade 1 in severity).

In terms of reported TEAEs, no imbalances of clinical relevance were noted between treatment arms in Part I of the PK study. Overall, none of the treatment-related TEAEs reported in either part of Study CT-P39 1.1 were unexpected and the reported safety findings after single dose administration in healthy subjects reflect the known safety profile of Xolair.

The Phase 3 study in CSU patients showed a comparable frequency of TEAEs across all treatment arms in the Overall Period Safety Set. A lower incidence of TEAEs considered related to the study drug was reported in the principal CT-P39 300 mg arm when compared to the Xolair 300 mg arm. The majority of TEAEs were considered mild to moderate in severity.

Although one death was reported in the CT-P39 300 mg arm, this was considered unrelated to the study drug. A higher number of TESAEs were reported in the CT-P39 300 mg, but no TESAEs (by PT) were reported for more than 1 patient. Those considered possibly related to CT-P39 were of a grade 2 or grade 3 intensity. The reported incidence of TEAESIs was low in the study and generally lower in CT-P39 treatment groups.

On evaluation of the full safety data in CSU patients, CT-P39 appears to have a comparable safety profile with that of the reference product in terms of type, frequency, severity, and relatedness of TEAEs. There were no unexpected findings which would indicate a difference in safety profiles between both CT-P39 and the originator.

Immunogenicity

In Study CT-P39 1.1 (Part 1), the incidence of post-treatment ADA was lower in the CT-P39 group than the EU-approved Xolair group. NAb was not detected in the CT-P39 group and was detected in 1 subject in the EU-approved Xolair group. There was no subject with an increasing trend in ADA titre after treatment, and the majority had low ADA titer values. No immune-related AEs were reported in subjects with ADA positive results in Study CT-P39 1.1.

In Study CT-P39 3.1 in CSU patients, the incidence of post-treatment ADA was generally low at all timepoints. Titer values were generally low. One immune-mediated AE was reported post-ADA detection in the CT-P39 150/300 treatment arm at Week 24 (EOT), and this was considered to be unrelated to the study drug. The study was supportive of the reported relatively low incidence of ADA development in CSU patients, as shown with Xolair.

Despite differing trends in ADA detection between both clinical studies and between treatment periods within the Phase 3 study, there were no notable differences in the overall safety profile of CT-P39 and Xolair observed when evaluated according to ADA status. Differences in immunogenicity did not correlate to clinically significant differences in efficacy or safety between CT-P39 and Xolair.

3.3. Uncertainties and limitations about biosimilarity

Quality aspect

Overall, based on the quality data presented, the claim of biosimilarity is supported.

Clinical aspects

Efficacy

Overall, based on the clinical data presented, the claim of biosimilarity is supported.

There were concerns with respect to the apparent lack of dose response with CT-P39, as no significant differences in efficacy were shown in the pivotal study CT-P39 3.1 in patients with chronic urticaria between the 150 mg and 300 mg dose. However, based on the provided additional analyses, it is agreed that the absence of the apparent dose-response in CT-P39 does not imply a treatment difference between CT-P39 and Xolair, considering the modest dose-response in Xolair and the compelling dose-relationship in PK and PD profiles. Further, it appears that the patients with low baseline IgE in CT P39 150 mg treatment group impacted on the overall results with their unexpected high responses, leading to the picture of a missing dose-response for CT-P39. While some uncertainty whether CT-P39 exhibits the same dose response as seen for Xolair remains, taking into consideration the totality of the data, it is considered that this uncertainty should not preclude a positive conclusion on the biosimilarity between CT-P39 300 mg and Xolair 300 mg.

3.4. Discussion on biosimilarity

Analytical similarity of CT-P39 was assessed in a comprehensive similarity exercise using EU-sourced Xolair as the Reference Medicinal Product. The comparability assessment was, for the most part, conducted as per the relevant EU guidelines on the development of similar biological medicinal products (CHMP/437/04 Rev 1, EMA/CHMP/BWP/247713/2012) and only a few minor queries were raised and resolved during the procedure. The quality attributes analysed are considered suitable to compare the most relevant physicochemical and biological quality attributes of the Omalizumab molecule and were shown to be highly similar between CT-P39 and EU-approved Xolair.

Overall, the comparative analytical assessment demonstrated that the primary and higher order structure, functional binding, and bioactivity of CT-P39 is highly comparable to EU-approved Xolair. For C-terminal lysine variants, charge, and purity/impurities, some minor differences were observed. However, any differences identified were considered minor and were in general sufficiently justified by the applicant and have no clinically meaningful impact, hence do not impact on the biosimilarity claim.

In the PK study in healthy volunteers, biosimilarity has been demonstrated according to the pre-specified acceptance criteria; the GMRs and 90% CIs were within the 80-125% acceptance criteria for the primary PK endpoints of $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}. PK biosimilarity for CT-P39 with EU-approved Xolair can be accepted.

In the efficacy and safety study CT-P39 3.1, CT-P39 demonstrated similar efficacy as EU-approved Xolair in primary and secondary efficacy endpoints.

The primary endpoint, change from Baseline in Weekly Itch Severity Score at week 12 was met. Although a slightly better response and therefore lower ISS7 score was reported in patients receiving treatment with 300 mg Xolair (at week 12 a change from baseline in ISS7 was - 9.98 in this group) as compared to those treated with 300 mg CT-P39 (at week 12 ISS7 was -9.21), the 95% CI of treatment difference in the mean was [-0.37, 1.90] which was within the predefined equivalence margin of [-2.0, 2.0].

With regards to safety data presented from the PK and efficacy studies, no clinically relevant differences have been detected that would indicate dissimilarity between the safety profiles of CT-P39 and EU-approved Xolair. No notable imbalances were observed with respect to type, severity, or relatedness of reported TEAEs between treatment groups in either study. No emerging safety signals were reported, and data were generally in line with the known safety profile of EU-approved Xolair.

On the basis of immunogenicity data submitted and with consideration to the totality of evidence presented (including quality, non-clinical and clinical data), the observed difference in immunogenicity (as measured by post-treatment ADA status) between CT-P39 with EU-approved Xolair has not resulted in any clinically significant dissimilarity between the two products.

3.5. Extrapolation of safety and efficacy

Celltrion is seeking approval for CT-P39 for the same indications approved for the reference medicinal product Xolair:

- Allergic asthma in adults, adolescents (12 years and above) and children (6 to <12 years of age)
- Chronic rhinosinusitis with nasal polyps in adults (18 years and above)
- Chronic spontaneous urticaria in adult and adolescent (12 years and above)

Mechanism of action for omalizumab-binding to IgE and preventing binding of IgE to FcεRI (high-affinity IgE receptor) on basophils and mast cells, thereby reducing the amount of free IgE that is available to trigger the allergic cascade, is the common MoA in each of the originator indications.

The pivotal efficacy and safety study (CT-P39 3.1) supporting this application was performed in patients with chronic spontaneous urticaria (CSU) who remain symptomatic despite H1-antihistamine treatment, which was agreed during the SA. Population of patients with CSU was considered as more homogenous and therefore a more sensitive than population of patients with allergic asthma, and therefore acceptable to be used in the pivotal efficacy study supporting this biosimilar application. Taking into consideration the same mechanism of action of omalizumab and consistent PK profile across all the sought indications, the extrapolation from CSU to chronic rhinosinusitis with nasal polyps is also considered acceptable.

3.6. Additional considerations

Having considered the final recommendation of the inspection team, the CHMP does not consider that the issues identified during the GCP inspection have a significant impact on the benefit-risk balance for Omlyclo.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Omlyclo is considered biosimilar to Xolair. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Omlyclo is favourable in the following indication(s):

Allergic asthma

Omlyclo is indicated in adults, adolescents and children (6 to <12 years of age).

Omlyclo treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma (see section 4.2).

Adults and adolescents (12 years of age and older)

Omlyclo is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

Children (6 to <12 years of age)

Omlyclo is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

Chronic rhinosinusitis with nasal polyps (CRSwNP)

Omlyclo is indicated as an add-on therapy with intranasal corticosteroids (INC) for the treatment of adults (18 years and above) with severe CRSwNP for whom therapy with INC does not provide adequate disease control.

Chronic spontaneous urticaria (CSU)

Omlyclo is indicated as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

to be implemented by the Member States

Not applicable.