



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2024
EMA/328491/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Steqeyma

International non-proprietary name: ustekinumab

Procedure No. EMEA/H/C/005918/0000

Note

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



Administrative information

Name of the medicinal product:	Steqeyma
Applicant:	Celltrion Healthcare Hungary Kft. Westend Office Building B Torony Vaci Ut 1-3 1062 Budapest HUNGARY
Active substance:	ustekinumab
International Non-proprietary Name/Common Name:	ustekinumab
Pharmaco-therapeutic group (ATC Code):	Immunosuppressants, interleukin inhibitors (L04AC05)
Therapeutic indication(s):	<u>Plaque psoriasis</u> Steqeyma is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1). <u>Paediatric plaque psoriasis</u> Steqeyma is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies (see section 5.1). <u>Psoriatic arthritis (PsA)</u> Steqeyma, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1). <u>Crohn's Disease</u> Steqeyma is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an

	inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF α antagonist or have medical contraindications to such therapies.
Pharmaceutical form(s):	Concentrate for solution for infusion; Solution for injection
Strength(s):	45 mg, 90 mg and 130 mg
Route(s) of administration:	Intravenous use and subcutaneous use
Packaging:	pre-filled syringe (glass) and vial (glass)
Package size(s):	1 pre-filled syringe and 1 vial

Table of contents

1. Background information on the procedure	9
1.1. Submission of the dossier.....	9
1.2. Legal basis, dossier content.....	9
1.3. Information on paediatric requirements.....	10
1.4. Information relating to orphan market exclusivity.....	11
1.4.1. Similarity.....	11
1.5. Scientific advice	11
1.6. Steps taken for the assessment of the product.....	11
2. Scientific discussion	13
2.1. Problem statement	13
2.2. About the product	13
2.3. Type of application and aspects on development	13
2.1. Quality aspects	13
2.1.1. Introduction.....	13
2.1.2. Active Substance	14
2.1.3. Finished Medicinal Product	17
2.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects.....	25
2.1.5. Conclusions on the chemical, pharmaceutical and biological aspects	25
2.2. Non-clinical aspects	26
2.2.1. Introduction.....	26
2.2.2. Pharmacology	26
2.2.3. Pharmacokinetics.....	26
2.2.4. Toxicology	27
2.2.5. Ecotoxicity/environmental risk assessment	28
2.2.6. Discussion on non-clinical aspects.....	28
2.2.7. Conclusion on the non-clinical aspects.....	28
2.3. Clinical aspects	29
2.3.1. Introduction.....	29
2.3.2. Clinical pharmacology	30
Study CT-P43 1.1	31
<i>Results</i>	32
2.3.3. Discussion on clinical pharmacology.....	52
2.3.4. Conclusions on clinical pharmacology	55
2.3.5. Clinical efficacy	56
2.3.6. Discussion on clinical efficacy	85
2.3.7. Conclusions on the clinical efficacy.....	87
2.3.8. Clinical safety.....	87
2.3.9. Discussion on clinical safety	114
2.3.10. Conclusions on the clinical safety	120
2.4. Risk Management Plan	120
2.4.1. Safety concerns.....	120
2.4.2. Pharmacovigilance plan	121
2.4.3. Risk minimisation measures.....	122

2.4.4. Conclusion	125
2.5. Pharmacovigilance.....	125
2.5.1. Pharmacovigilance system	125
2.5.2. Periodic Safety Update Reports submission requirements	125
2.6. Product information	125
2.6.1. User consultation.....	125
2.6.2. Additional monitoring	125
3. Biosimilarity assessment.....	126
3.1. Comparability exercise and indications claimed	126
3.2. Results supporting biosimilarity	127
3.3. Uncertainties and limitations about biosimilarity	129
3.4. Discussion on biosimilarity.....	129
3.5. Extrapolation of safety and efficacy	130
3.6. Additional considerations.....	130
3.7. Conclusions on biosimilarity and benefit risk balance	130
4. Recommendations	131

List of abbreviations

Term	Explanation
λ_z	Terminal elimination rate constant
%AUC _{extrap}	Area under the concentration-time curve extrapolated from time zero to infinity as a percentage of total area under the concentration-time curve
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
ATC	Anatomical therapeutic chemical classification system
AUC	Area under the concentration-time curve
AUC _{0-inf}	Area under the concentration-time curve from zero to infinity
AUC _{0-last}	Area under the concentration-time curve from zero to the last quantifiable concentration
BASG	Bundesamt für Sicherheit im Gesundheitswesen
BLQ	Below the lower limit of quantitation
BMI	Body mass index
BP	Blood pressure
BPD	Biological product development
BSA	Body surface area
CAS	Chemical abstracts service
CD	Crohn's disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL/F	Apparent clearance after subcutaneous dosing
C _{max}	Maximum serum concentration
CMC	Chemistry, manufacturing and control
CRO	Contract research organisations
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CV%	Percent of coefficient of variance
DLQI	Dermatology Life Quality Index
DMARD	Disease-modifying anti-rheumatic drug
DP	Drug product
DRM	Data review meeting
DSMB	Data safety monitoring board
ECG	Electrocardiogram
ECL	Electrochemiluminescent
EMA	European Medicine Agency
EOS	End-of-study
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good clinical practice

Term	Explanation
IgG	Immunoglobulin G
IGRA	Interferon- γ release assay
IL	Interleukin
IND	Investigational new drug
INN	International non-proprietary name
ISR	Injection site reaction
ITT	Intent-to-treat
IV	Intravenous
LLoQ	the lower limit of quantification
LS	Least squares
MAA	Marketing authorisation application
MAR	Missing at random
MoA	Mechanism of action
MSD	Meso scale discovery
MTX	Methotrexate
NAb	Neutralising antibody
NK	Natural killer
NRS-11	Numeric rating scale
PASI	Psoriasis Area and Severity Index
pAUC	partial area under the concentration-time curve
PD	Pharmacodynamics
PFS	Pre-filled syringe with safety guard
PHS	Public health service
PIP	Paediatric investigation plan
PK	Pharmacokinetics
PPS	Per-protocol set
Ps	Plaque psoriasis
PsA	Psoriatic arthritis
PT	Preferred term
QoL	Quality of life
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SmPC	Summaries of product characteristics
SOC	System organ class
SPA	Special protocol assessment
sPGA	Static physician's global assessment
$t_{1/2}$	Terminal elimination half-life
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TK	Toxicokinetics
T_{max}	Time to maximum serum concentration
TNF	Tumour necrosis factor

Term	Explanation
UC	Ulcerative colitis
UK	United Kingdom
US	United States
USPI	United States prescribing information
V_z/F	Apparent volume of distribution during the terminal phase
VAS	Visual analogue scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celltrion Healthcare Hungary Kft. submitted on 25 May 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Steqeyma, 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:

Plaque psoriasis

Steqeyma is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1).

Paediatric plaque psoriasis

Steqeyma is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies (see section 5.1).

Psoriatic arthritis (PsA)

Steqeyma, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1).

Crohn's disease

Steqeyma is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF α antagonist or have medical contraindications to such therapies.

The applicant initially also applied for the ulcerative colitis indication but during the assessment, they informed the EMA of their decision to delete the ulcerative colitis indication from the applied indications.

Steqeyma has been developed for subcutaneous and intravenous administration: 45 mg solution for injection in prefilled syringe (glass), 90 mg solution for injection in prefilled syringe (glass) and 130 mg concentrate for solution for infusion (vial).

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:
 - Stelara (Ustekinumab), 45 mg solution for injection,
 - Stelara (Ustekinumab), 45 mg solution for injection in pre-filled syringe,
 - Stelara (Ustekinumab), 90 mg solution for injection in pre-filled syringe and
 - Stelara (Ustekinumab) 130mg concentrate for solution for infusion.
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 15-01-2009
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/08/494/001, EU/1/08/494/003, EU/1/08/494/004, EU/1/08/494/005.

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

- Product name, strength, pharmaceutical form:
 - Stelara (Ustekinumab), 45 mg solution for injection in pre-filled syringe,
 - Stelara (Ustekinumab), 90 mg solution for injection in pre-filled syringe and
 - Stelara (Ustekinumab) 130mg concentrate for solution for infusion.
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 15-01-2009
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/08/494/003, EU/1/08/494/004, EU/1/08/494/005

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:
 - Stelara (Ustekinumab), 45 mg solution for injection in pre-filled syringe,
 - Stelara (Ustekinumab), 90 mg solution for injection in pre-filled syringe and
 - Stelara (Ustekinumab), 130mg concentrate for solution for infusion.
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 15-01-2009
- Marketing authorisation granted by: Union
- Marketing authorisation number(s): EU/1/08/494/003, EU/1/08/494/004, EU/1/08/494/005.
- Bioavailability study number(s): CT-P43 1.1, CT-P43 1.2 and CT-P43 3.1

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	SAWP co-ordinators
12 December 2019	EMA/H/SA/4320/1/2019/III	<i>André Elferink, Stephan Lehr</i>

The applicant received scientific advice on the development of ustekinumab biosimilar (CT-P43) for the treatment in same indications as the reference product Stelara from the CHMP on 12/12/2019 (EMA/H/SA/4320/1/2019/III). The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Adequacy of the overall quality, non-clinical, and clinical development.
- Extension of comparative non-clinical and clinical results obtained with 45 mg/0.5 mL pre-filled pen presentation to all other intended presentations of CT-P43.
- Comparability of the intended delivery devices of CT-P43 (pre-filled syringe and pre-filled syringe with safety guard) to the delivery devices of Stelara.
- Release and long-term stability test items for CT-P43 drug substance and drug products.
- Size of the planned safety database; extrapolation of clinical study results to all indications authorised for Stelara.
- Design of a randomised, double-blind, three-arm, parallel group, single-dose study to compare the pharmacokinetics, safety, and immunogenicity of three subcutaneous injection formulations of CT-P43 and Stelara in healthy subjects including study population, route and dose, two-part design, endpoints, sampling time points for immunogenicity and duration for PK and immunogenicity, sample size, equivalence margin.
- Design of a randomised, active-controlled, double-blind study to compare efficacy and safety of CT-P43 with Stelara in patients with moderate to severe plaque psoriasis including study population, primary efficacy endpoint, secondary endpoints, equivalence margin, sample size and power, drug administration by unblinded staff.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Jayne Crowe Co-Rapporteur: Simona Badoi

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	25 May 2023
The procedure started on	15 June 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 September 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	N/A
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	18 September 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	12 October 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 January 2024
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	26 February 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	07 March 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	21 March 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	28 May 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 June 2024
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
Methodology Working Party experts were convened to address questions raised by the CHMP on The CHMP considered the views of the Methodology Working Party as presented in the minutes of this meeting.	17 April 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 Steqeyma on	27 June 2024

2. Scientific discussion

2.1. Problem statement

Not applicable for biosimilars.

2.2. About the product

Ustekinumab is a fully human IgG1κ monoclonal antibody that binds to the p40 subunit of interleukin (IL) 12 and 23, thereby preventing them from binding to the IL-12Rβ1 receptor expressed on the surface of immune cells. By doing so, ustekinumab prevents the activation of the Th1 and Th17 cytokine pathways, which are central to the pathology of psoriasis, psoriatic arthritis and Crohn's disease.

Steqeyma has been developed for subcutaneous and intravenous administration: 45 mg solution for injection in prefilled syringe (glass), 90 mg solution for injection in prefilled syringe (glass) and 130 mg concentrate for solution for infusion (vial).

2.3. Type of application and aspects on development

Steqeyma (also called CT-P43 in the report) has been developed as a biosimilar to the EU reference product Stelara (INN: ustekinumab), which was authorised via the Centralised Procedure in the European Union on 15.01.2009.

During the development programme the applicant sought Scientific Advice from the BASG and from the EMA Scientific Advice Working Party (see section 1.5.).

2.1. Quality aspects

2.1.1. Introduction

Steqeyma (ustekinumab, also termed CT-P43) is a recombinant humanised monoclonal antibody (mAb) that has been developed as a similar biological medicinal product to the reference medicinal product, Stelara (EMA/H/C/000958).

CT-P43 specifically binds to p40 which is a subunit of IL-12 and IL-23 and prevents IL-12 and IL-23 from binding to IL-12Rβ1 receptor of natural killer (NK) and T cells. Thus, CT-P43 neutralises IL-12 (Th1) and IL-23 (Th17) mediated cellular responses that are associated with immune-mediated human diseases.

Steqeyma will be made available in the following dose forms, strengths, and pack sizes:

- 45 mg in 0.5 mL (90 mg/mL) solution in a single-dose pre-filled syringe with safety guard for subcutaneous injection (pack size: 1 pre-filled syringe)
- 90 mg in 1 mL (90 mg/mL) solution in a single-dose pre-filled syringe with safety guard for subcutaneous injection (pack size: 1 pre-filled syringe)
- 130 mg in 26 mL (5 mg/mL) solution in a single-dose vial for intravenous infusion (pack size: 1 vial)

The product is available in a 30 mL Type I borosilicate glass vial closed with a butyl rubber stopper for the vial presentation and in a 1-mL Type I borosilicate glass syringe with a 1/2-inch (27 G thin wall) staked stainless steel needle for the PFS presentations.

2.1.2. Active Substance

2.1.2.1. General information

Steqeyma (Ustekinumab) is a fully human IgG1k monoclonal antibody produced in a Chinese hamster ovary (CHO) cell line using recombinant DNA technology. It has one N-linked glycosylation site (Asn299) in the CH2 domain of each heavy chain. The theoretical molecular mass of the intact CT-P43 molecule is approximately 145.3 kDa.

Ustekinumab binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12R β 1 receptor protein expressed on the surface of immune cells. Details of antibody structure, mechanism of action (MoA) and the amino acid sequence is provided in the dossier.

2.1.2.2. Manufacture, process controls and characterisation

Manufacturers

Sites responsible for the manufacture, testing and release of CT-P43 active substance are provided. All manufacturing sites have been determined to be in compliance with GMP.

Description of manufacturing process and process controls

The manufacturing process and controls are considered to be well described. Acceptance criteria ranges or limits are provided for critical and non-critical parameters. A description of the batch numbering system has been adequately described.

Manufacturing starts from a vial of working cell bank (WCB), which is expanded through a series of flasks, seed train bioreactors into a production perfusion bioreactor. The purification process consists of a series of chromatography, low pH virus inactivation, viral filtration, ultrafiltration and diafiltration and the final fill of the active substance (AS). The manufacturing description for the purification stage is considered acceptable as the main aspects of the process are described.

Process flow diagrams have been provided for the various active substance unit operations.

Control of materials

The list of raw materials and their specifications has been provided for both the cell culture and purification stage. Compendial materials are listed with cross reference to the relevant Pharmacopoeia grade. Non compendial raw materials are tested in-house. The in-house specifications proposed are considered sufficient.

The host cell line is Chinese hamster ovary cells. The characteristics of the major genetic elements of the plasmid are described, the cDNA and amino acid sequence translated from the nucleotide sequence of the Steqeyma genes are provided. The construction process is described in line with Ph. Eur. 0784 products of recombinant DNA technology and in line with ICH Q5B. The top clone was used to produce the research cell bank and was used to produce a pre-master cell bank (MCB). From the pre-MCB a two-tiered cell banking system was developed consisting of a MCB and a WCB. Establishment and

characterisation of the MCB and WCB is described in accordance with the ICH Q5D. Appropriate testing has been done on the WCB and MCB in line with ICH Q5A and ICH Q5D.

An end of production cell bank (EPCB) was established from a commercial scale batch by the continued passages of cells that were derived from the production bioreactor at the time of harvest. The EPCB was tested in line with the requirements of ICH Q5A. The stability of the MCB beyond production is considered to be adequately supported.

Control of critical steps and intermediates

The control strategy development is considered to be well described. The quality target product profile (QTPP) is based on the finished product (FP) and critical quality attributes (CQAs) have been established for the AS based on this profile and are considered appropriate. The critical process parameters (CPP) and relevant CQA affected by the process parameter are listed in the dossier.

Process validation.

Process validation for CT-P43 AS was carried out at commercial scale at the intended commercial manufacturing site.

Hold time validation has been performed.

Overall, the applicant has provided sufficient data to provide assurance that the manufacturing process is appropriately validated and can produce active substance batches of consistent quality.

Manufacturing process development

The applicant made a number of changes to the manufacturing process throughout the development to optimise the process.

The applicant has also highlighted the changes made to the release specifications and analytical methods used throughout the process development. The changes to the release specifications have mainly been tightening of the specifications as process knowledge has been gained and batch data. The majority of analytical methods have not changed.

The applicant used a risk assessment to evaluate the criticality of each process parameter on the CQAs, this is in line with ICH Q9 and is considered acceptable. The risk assessment is considered comprehensive and identified the critical process parameters. These parameters were studied for their potential impact on CQAs, the studies are considered sufficient. The applicant has provided the method validation summaries for all the analytical methods used for critical in process testing of the active substance. All the methods were validated for the sample matrix. All methods are considered fit for purpose.

Overall, the changes throughout the manufacturing process have been adequately described. Information and data have been provided to support how the control strategy was developed and is considered acceptable. An acceptable approach for demonstrating comparability between the different processes used to produce the AS shows there are no significant differences noted between the quality attributes tested that would affect safety or efficacy.

Characterisation

Characterisation is provided using state of the art methods with the AS process performance qualification (PPQ) batches, pre-filled syringe (PFS) FP batches and intravenous (IV) FP batches. To ensure manufacturing does not affect the quality profile, the AS and FP batches were evaluated in side-by-side tests.

The data shows that there is no difference in product quality for the AS and the FP presentations. The approach is 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. Overall, the characterisation studies have been carried out in a very comprehensive manner and covers all relevant aspects for a monoclonal antibody.

Impurities

A detailed description of the potential product- and process-related impurities has been provided.

2.1.2.3. Specification

The proposed panel of release tests cover identity, quantity, purity/impurity, potency, general tests, charge heterogeneity, glycosylation and safety. In general, the panel of tests are in line with ICH Q6B and are considered appropriate for routine control of a monoclonal antibody at release.

Analytical procedures

Compendial analytical procedures are performed in accordance with the relevant Ph. Eur. monographs.

The non-compendial method descriptions are sufficiently detailed and include details regarding equipment, reagents, operating conditions, sample and standard preparation, assay controls and system of suitability.

The analytical procedures have been appropriately validated in accordance with ICH Q2(R1). Verification data has been presented for all the compendial methods and the data presented shows that all the verification results met the acceptance criteria and the methods are considered appropriate for their intended use.

For the non-compendial methods, a summary of the validation results for each method has been submitted.

Batch analysis

Batch analysis data is provided for non-clinical batches (process A), engineering batch, clinical batches and PPQ batches. All batches comply with the specifications in place at the time of testing. The data demonstrate that the commercial process is capable of manufacturing a consistent active substance.

Justification of specification

The specifications have been based on batch analysis data of CT-P43 AS batches. The limits are deemed acceptable.

Reference standards

The applicant has established reference standards throughout the development of CT-P43 which included preliminary reference standard, primary reference standard and working reference standard.

Container closure

The container closure systems for the CT-P43 AS are pre-sterilised (gamma irradiated), pyrogen free polycarbonate bottles. Representative certificates of analysis from the vendor are provided. The specifications for the container closure system have been provided. In addition, diagrams have been provided which highlight the dimensions of the container.

2.1.2.4. Stability

Stability studies have been performed in accordance with ICH guidelines in terms of testing frequency and storage conditions using validated methods.

A shelf-life for the CT-P43 AS stored at long-term condition at 36 months was proposed based on the long-term, intermediate and accelerated stability data of the clinical batches. Considering the stability data, the comparability data provided and the manufacturing process being identical between the clinical and the commercial batches, the proposed shelf-life is considered acceptable.

2.1.3. Finished Medicinal Product

2.1.3.1. Description of the product and pharmaceutical development

There are three dosage forms of CT-P43: two prefilled syringes for subcutaneous administration (45 mg and 90 mg) and a concentrate for solution for infusion (130 mg).

CT-P43 finished product is formulated for subcutaneous (SC) administration as a sterile, preservative-free liquid solution in a pre-filled syringe intended to deliver 45 mg or 90 mg of CT-P43 active substance. Each syringe is designed to deliver a single dose of 45 mg or 90 mg CT-P43 active substance in a 0.5 mL or 1.0 mL of solution at a concentration of 90 mg/mL.

CT-P43 finished product is formulated for intravenous (IV) administration as a sterile, preservative-free liquid solution containing 130 mg of CT-P43 active substance. Each vial is designed to deliver a single dose of 130 mg CT-P43 active substance in a 26 mL of solution at a concentration of 5 mg/mL.

The finished product for subcutaneous administration contains the active substance (ustekinumab), L-histidine, L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80, and water for injection.

The finished product for intravenous administration contains the active substance (ustekinumab), L-histidine, L-histidine monohydrochloride monohydrate, EDTA disodium salt dihydrate, L-methionine, sucrose, polysorbate 80, and water for injection.

Pharmaceutical development

Full details of the formulation history throughout clinical development are 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-P43 subcutaneous syringe (SCS) aligned with the reference medicinal product (RMP), Stelara, throughout development.

The commercial formulation for both SCS were used in phase III clinical trials. No novel or excipients are used. The selection of excipients and their concentrations are based on internal knowledge/experience, development studies and shipping and freeze/thaw studies. The formulation of the intravenous vial (IVV) differs from that of the RMP and from the formulation presented in the formulation development study. The applicant has presented a good understanding of each component used in the commercial formulation of both forms and justified their inclusion.

Manufacturing process development

Manufacturing process development from the early development phase to the commercial production is clearly described. Comparability is presented throughout the development.

Comparability assessments included extended characterisation incorporating primary, secondary and tertiary structural analysis, biological activity and release testing. A summary of the comparability studies has been provided and the presented data has demonstrated comparability.

Characterisation of impurities

An acceptable risk assessment on nitrosamine impurities has been provided. 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). An acceptable risk assessment of elemental impurities has been provided in line with ICH Q3D.

Container closure

The primary container closure system for CT-P43 45 mg and 90 mg SCS finished product is a 1-mL Type I borosilicate glass syringe with a 1/2-inch (27 G thin wall) staked stainless steel needle. The syringe is closed with a siliconised elastomeric (bromobutyl) plunger stopper and has an elastomeric needle shield (cap). The components of CT-P43 primary packaging comply with the requirements of the relevant Ph. Eur. monographs and ISO 10993. The choice of container closure system for CT-P43 quality and safety has been demonstrated and is supported by functionality (break-loose glide force) and compatibility studies.

The primary container closure system for CT-P43 130 mg IVV finished product is composed of a 30-mL type I glass vial, a 20-mm rubber stopper, and a 20-mm flip-off cap. The information provided on the development of the CC for the vial is adequate.

Bioburden and endotoxins are routinely tested as in-process controls (IPCs) and critical IPCs for all dosage forms. Sterility and endotoxins are tested at release and over shelf-life. Validation data is provided which supports integrity of the containers, and stability data demonstrates that the integrity of the container closure system is maintained throughout the shelf life.

2.1.3.2. Manufacture of the product and process controls

Manufacturers

Sites responsible for the manufacture, testing and release of CT-P43 finished product are provided.

All manufacturing sites have been determined to be in compliance with GMP.

Process controls

The manufacturing process for the SCS and IVV have similar control strategies which are controlled by several CPPs and IPCs.

Process validation / verification

Process validation was performed on commercial scale batches each for the PFS 45 mg and 90 mg and vial 130 mg.

For each dosage form, for each process step, the at-scale PV lots met acceptance criteria for CPPs and IPCs registered in P.3.3. Media fill runs have been performed and demonstrate that asepsis is maintained during the fill step. A bacterial challenge study was performed on the sterilising filter using an appropriate organism.

Sterilisation of the vial primary packaging has been performed and validation of the autoclaving and dry-heat tunnel process has been suitably performed.

Process consistency was performed and extensive characterisation and release tests showed that the process produced a consistent product throughout.

Shipping validation of CT-P43 FP via air and ground transportation under refrigerated conditions is considered acceptable.

The data provided demonstrates that the FP manufacturing process is valid, under control and capable of producing material of consistent quality.

2.1.3.3. Product specification

The finished product specifications include control of identity, purity and impurities, potency, sterility and other general tests.

Analytical procedures and reference standards

The specifications are generally acceptable. Queries were raised during the procedure and adequately addressed.

The method descriptions are concise and described in sufficient detail. All other analytical procedures are either common to testing of both AS and FP and thus provided in Active Substance Section 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, product specific qualification is performed and show CT-P43 does not interfere with method performance. The finished device specific methods were also suitably validated.

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 are the same and because the AS is essentially the same as the FP from a quality perspective. FP specific method acceptance criteria are aligned with Ph. Eur. or are based on batch data and considered generally acceptable.

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 is provided for 45 mg FP lots manufactured from SCS processes 1, 2 and 3. Batch data has also been provided for batches of the 90 mg process SCS-2 and SCS-3. batches of the 130 mg IVV FP have provided, from Process IVV-1 and IVV-2 (current commercial). Results from all FP strengths batches show consistency and uniformity of the finished product and indicate that the process is under control

The applicant has been requested to provide the results of release tests performed on the assembled SCS FP.

Container closure (see also above)

The primary packaging for the CT-P43 SCS FP consists of a 1mL long glass PFS fitted with a staked 27G, ½" special thin wall needle. In general, adequate descriptions have been provided for the container closure system components, including supplier specifications, technical drawings and dimensions. The applicant notes that the staked needle is sterilised with ethylene oxide and the.

Further details on the sterilisation methods are provided in the certificate of analysis for each component provided, which confirm sterilisation can achieve a sterility assurance level, SAL of 10^{-6} .

The primary container closure for CT-P43 130 mg IVV is composed of vial, stopper, and seal as primary packaging components.

The glass barrels 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.

A Notified Body Opinions (NBOp) from BSI has been supplied for the PFS confirming full compliance with the relevant General safety and Performance Requirements (GSPRs).

2.1.3.4. Stability of the product

The proposed shelf-life of CT-P43 is 36 months when stored under refrigerated conditions (2-8°C). SmPC labelling states that the product should not be frozen and protected from light. An in-use shelf life based on stability data for the vials and PFS allows for a period of 31 days at room temperature (up to 30°C) after long term storage at 5°C.

Stability studies are carried out in accordance with current ICH guidelines. The proposed shelf life of CT-P43 is 36 months and is supported.

Results of the stability data to date of supporting and production batches fall within the acceptance criteria tested under long term storage conditions (5°C). Trending data over these batches shows the product is stable (no changes over time). In both process 2 and process 3 batches increases in acidic variants were observed, however remained with specification.

Stability of all dosage forms at room temperature (up to 30°C) after long term storage at 5°C was evaluated and the results confirm that CT-P43 is stable for up to 31 days at room temperature when removed from refrigerated conditions.

The proposed shelf life is further supported with data from accelerated and stressed studies. Purity analysis revealed product degradation under both accelerated and stressed conditions, as expected.

A photostability study, performed according to ICH Q1B, demonstrating that CT-P43 is sensitive to light exposure, the applicant has confirmed that a special precaution will be included in the product information.

Stability of the IVV following dilution in 0.9% Sodium Chloride contained in a polypropylene bag has been provided and the in-use stability is supported.

The accepted shelf life for the PFS and unopened vial is 3 years at 2°C-8 °C.

2.1.3.5. Biosimilarity

CT-P43 has been developed as a biosimilar to both EU Stelara for subcutaneous (SC) injection in pre-filled syringe (PFS) and EU Stelara for intravenous (IV) formulation for infusion in a vial. Analytical similarity of CT-P43 was assessed in a comprehensive similarity exercise using EU-sourced Stelara 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.

Biosimilarity of Pre-filled syringe presentation

Selection of batches – PFS

The applicant has presented summary tables of all test CT-P43 and RMP batches used in the biosimilarity exercise allowing ease of assessment. The 2-way analysis included several batches of EU Stelara (Eight 45 mg, two 90 mg), and several batches of CT-P43 (four AS batches, four 45 mg FP, two 90 mg FP). The applicant has included batches of CT-P43 and EU Stelara which were used in the clinical studies, which is endorsed. The number of lots used is expected to reflect variability sufficiently and is deemed acceptable for evaluation of similarity. The applicant clearly states that all batches used in the comparative assessment were stored and handled as per the approved conditions.

Two-way similarity assessment – PFS

The similarity ranges were established using data from analysis of several EU Stelara batches.

The selected comprehensive set of orthogonal state-of-the-art analytical methods are adequate to address the relevant quality attributes of ustekinumab.

Biosimilarity of vial presentation

Selection of batches – vial

The 2-way analysis included several batches of each EU Stelara and CT-P43 130mg/vial. The age of batches at the time of testing is provided and are considered well spread with sufficient overlap between both products. The same approach was used as for the PFS where only key biological assays related to efficacy, PK and the known and putative mechanisms of action of ustekinumab were included in statistical analysis.

Two-way analytical similarity – vial

The results of the biosimilarity exercise are presented in the dossier in the same manner as for the PFS, with summary tables of the individual data points, mean and SD, and graphs where relevant for each quality attribute, allowing ease of assessment of the analytical similarity of CT-P43 IV (vial) to EU Stelara IV (vial). In general, the results are aligned with those observed in the PFS similarity exercise and support a conclusion of biosimilarity.

Additional characterisation/forced degradation (vial and PFS)

Additional characterisation and additional MoA studies were performed with a limited number of batches. For the purpose of supportive studies, testing of a reduced number of lots is deemed acceptable. These complementary studies are adequately designed to support the conclusions drawn by the applicant that any differences observed in the comparative assessment have no significant impact on biological activities and therefore have no clinically meaningful impact. Hence, inclusion of these studies is endorsed. The forced degradation study was also performed, and the results show that the degradation trends are in general similar between the two products.

Analytical Methods (Vial and PFS)

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. While no qualification information is provided for the methods used for ADCC and CDC activity, no queries are raised as these assays are not critical to the mechanism of action.

Table 1. Biosimilarity exercise: analytical comparability tests and conclusions

Attribute		Method	Similarity Conclusion
Primary Structure	Amino acid sequence	Peptide Mapping by LC/MS	Identical amino acid sequence (100% sequence coverage) for CT-P43 and Stelara.
	Intact Mass	LC/MS	Reduced and non-reduced intact mass analysis yielded similar masses of Stelara and CT-P43.
	Reduced Mass	LC/MS	
Post-translational modifications	Deamidation (%)	Peptide mapping (LC-MS)	CT-P43 has similar deamidation levels to Stelara.
	Oxidation (%)	Peptide mapping (LC-MS)	Oxidation levels in CT-P43 were slightly higher than in Stelara. The differences are marginal (<1%).
	N-terminal Glutamic Acid Variant (%)	Peptide mapping (LC-MS)	CT-P43 has similar level of N-terminal variants to Stelara.
	C-terminal Variant (%)	Peptide mapping (LC-MS)	CT-P43 has slightly higher levels of C-terminal variants compared to Stelara. Literature indicate that they have no impact on biological activity, PK, immunogenicity, or safety.
	Isomerization (%)	Peptide mapping (LC-MS)	CT-P43 has similar isomerisation level compared to Stelara.
Higher order structure	Secondary	FITR, far UV	Similar secondary structure for CT-P43 and Stelara.
	Tertiary	DSC, near UV	Similar tertiary structure, thermal unfolding profiles and thermal transition midpoint temperatures indicating that the thermal stability and conformation of Stelara and CT-P43 are highly similar.
	Disulphide Bonds	Native and reduced peptide mapping	Identical disulfide bond connectivity demonstrated for CT-P43 and Stelara.
	Free Thiol	Ellman's assay	Similar free thiol content for CT-P43 and Stelara.
Glycation and Glycosylation	Glycation	LC/MS after deglycosylation and reduction	A slightly higher level of glycation was observed in CT-P43 compared to Stelara but not expected to have an adverse effect on clinical safety, efficacy, PK, or immunogenicity.
	Oligosaccharide Profiling	HILIC-UPLC-FLD	CT-P43 was shown to have minor differences in oligosaccharide profiles compared to EU-Stelara, but it has been sufficiently justified that these differences are highly unlikely to be of clinical relevance.
	N-linked Glycan Analysis	LC/MS	
	Sialic Acid Analysis	HPLC	
Physicochemical analyses	Charge Variants	cIEF	The cIEF electropherograms showed a slightly different pattern between CT-P43 and Stelara. The differences observed are not considered clinically meaningful.
	Charge Variants	IEC-HPLC	The Charge Variants showed a slightly different pattern between CT-P43 and Stelara. The differences observed are not considered clinically meaningful.

	Protein content	UV280	Stelara and CT-P43 had highly similar protein concentrations. The statistical analysis showed that all lots of CT-P43 were within the quality range of Stelara.
	Size variants	SEC-HPLC	CT-P43 was shown to have minor differences in size variants and purity/impurity compared to EU-Stelara, but it has been sufficiently justified that these differences are highly unlikely to be of clinical relevance.
		SEC-MALS	
		AUC	
	Purity/impurities	CE-SDS (reduced)	
		CE-SDS (non-reduced)	
Functional Activity	Potency Biological Activity (Fab Binding)	IL-12/IL-23 p40 Binding Assay	Similar p40 binding for CT-P43 and Stelara. All lots of CT-P43 were within the quality range of Stelara.
		Cell-based hIL-12 Binding Inhibition Assay	Similar hIL-12 binding inhibition for CT-P43 and Stelara. All lots of CT-P43 were within the quality range of Stelara.
		Cell-based hIL-23 Binding Inhibition Assay	Similar hIL-23 binding inhibition for CT-P43 and Stelara. All lots of CT-P43 were within the quality range of Stelara.
		hIL-12 Mediated Signalling Inhibition Activity	Similar hIL-12 inhibition activity for CT-P43 and Stelara. All lots of CT-P43 were within the quality range of Stelara.
		hIL-23 Mediated Signalling Inhibition Activity	Similar hIL-23 inhibition activity for CT-P43 and Stelara. All lots of CT-P43 were within the quality range of Stelara.
		IFN- γ Secretion Inhibition Activity	Similar inhibition of hIL-12-induced IFN- γ secretion by PBMCs for CT-P43 and Stelara. All lots of CT-P43 were within the quality range of Stelara.
	Biological Activity (Fc Binding)	C1q Binding Activity	The two products are highly similar in their C1q binding.
		Fc γ RIIIa (V-type) Binding Affinity (SPR)	CT-P43 showed lower binding affinities for all Fc γ receptors. However, the slightly lower Fc γ R binding affinities of CT-P43 are unlikely to have an adverse impact <i>in vivo</i> .
		Fc γ RIIIb Binding Affinity (SPR)	
		Fc γ RIIa Binding Affinity (SPR)	
		Fc γ RIIb Binding Affinity (SPR)	
		Fc γ RI Binding Affinity (SPR)	CT-P43 trends slightly lower than Stelara, however all lots of CT-P43 were within the quality range of Stelara lots. Any difference is likely due to analytical variability and is not considered to have any potential clinically meaningful impact in terms of PK profile.
		FcRn Binding Affinity	
		ADCC	No ADCC induction was observed for any CT-P43 or Stelara batch analysed.

		CDC	No CDC induction was observed for any CT-P43 or Stelara batch analysed.
--	--	-----	---

Overall conclusions

The applicant has performed a sound and comprehensive analytical biosimilarity exercise in line with EMA/CHMP/BWP/247713/2012 guidance. A sufficient number of lots, which can be expected to sufficiently reflect product variability of both the proposed biosimilar and the reference product, was included. The CT-P43 lots have been manufactured according to the clinical or intended commercial process and batches used in the clinical studies were included. The applicants chosen comparability approach of ± 3 SD comparability criteria for key biological attributes and a purely descriptive comparison of physicochemical attributes was found to be acceptable. The analytical results are clearly presented including chromatograms, spectra, response curves, with detailed summary tables of results for the individual batches enable an independent assessment of biosimilarity regardless of the statistical approach taken hence no queries are raised.

In general, the quality attributes analysed were shown to be highly similar between CT-P43 and EU Stelara. A large panel of relevant methods has been used to characterise and compare the most relevant physicochemical and biological quality attributes of the ustekinumab molecule. Overall, the comparative analytical assessment demonstrated that the primary and higher order structure, functional binding, and bioactivity of CT-P43 is highly comparable to EU Stelara. While there are some notable differences in C-terminal lysine variants, charge variants and glycan map profiles for CT-P43 compared to EU Stelara, these have been described in detail, with any potential clinical implications adequately discussed. The observed differences are in general justified by the difference in cell lines and are not considered clinically significant and hence do not impact on the biosimilarity claim.

Supportive characterisation data is also present from a reduced number of lots to support the conclusions drawn by the applicant that any differences observed in the comparative assessment have no significant impact on biological activities and therefore have no clinically meaningful impact.

Overall, biosimilarity with EU Stelara is considered demonstrated from a quality point of view.

2.1.3.6. Adventitious agents

The strategy consists of controlling potential sources of virus contamination both in the cell bank system and the production process, and viral clearance processes. 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. The study reports including raw data for the MCB, WCB and EPCB virus testing have been requested. The unprocessed bulk is tested for mycoplasma in accordance with the Ph. Eur. 2.6.7 or Ph. Eur. 5.1.6. No materials of human origin are used during routine manufacture. An acceptable viral and TSE risk assessment has been provided for the materials of animal origin used during routine cell culture or cell banking. The applicant's conclusion that there is a minimal risk of TSE contamination can be supported.

Testing on the unprocessed bulk included adventitious virus testing and the results are acceptable.

A summary of the viral clearance studies has been provided and in general is acceptable and complies with ICH Q5A.

Overall, the results of viral clearance study demonstrated that the production process has sufficient capacity to inactivate or remove viruses.

Overall, adventitious agents safety is considered sufficiently assured.

2.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The active substance manufacturing process is standard for the production of monoclonal antibodies. Details of developmental genetics and the establishment of the MCB and WCB are described and acceptable. The control strategy for the active substance is comprehensive with sufficient control of each manufacturing step. The manufacturing process has been appropriately validated. The lists of raw materials have been provided and are acceptable. The characterisation data presented was comprehensive. The panel of release tests covers relevant aspects of purity, potency, and safety. Batch data provided demonstrate that the commercial process is capable of manufacturing a consistent active substance. Reference standards are sufficiently described. The container closure systems for the AS are a pre-sterilised (gamma-irradiated), pyrogen free polycarbonate bottles. A shelf-life for the CT-P43 AS stored at long-term condition at 36 months is considered acceptable.

Overall, the CT-P43 finished product is of high quality and the documentation provided for the manufacture, control and stability of the finished product is sufficiently detailed. The finished product is presented as a sterile, preservative-free solution in a 1mL Type I glass pre-filled syringe or a 30mL Type I borosilicate glass vial. The product is formulated using commonly used excipients. Sufficient details are provided detailing the pharmaceutical and development of the product. Data presented throughout the process development confirm that quality of the FP was consistently maintained or improved during development and that the commercial product is the same as batches used in clinical studies. The product is manufactured under GMP, and the manufacturing process consists of formulation, sterile filtration, aseptic filling, and visual inspection processes. The proposed batch sizes of the 45 mg, 90 mg and 130 mg products are sufficiently supported by validation data. The processes are well described, and process validation data supports the proposed process. Release and stability specifications, for the most part, ensure adequate control of the product. The methods are suitably validated. The primary packaging is supplied sterile or in the case of the vial is sterilised in-house. The proposed shelf life of 36 months for the IVV and SCS is supported by stability data.

Comprehensive comparability data have been provided and the claim of biosimilarity with EU Stelara is supported.

2.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Steqyma is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

No further recommendations for future quality development have been made.

In conclusion, based on the review of the quality data provided, it is considered that the marketing authorisation application for Steqyma is approvable from the quality point of view.

2.2. Non-clinical aspects

2.2.1. Introduction

The non-clinical development programme included *in vitro* primary pharmacodynamic (PD) studies and an *in vivo* 4-week repeat-dose toxicology study with toxicokinetic (TK) assessment in cynomolgus monkeys to compare Steqeyma with EU-approved Stelara. The conduct of repeated dose toxicity studies is not required for filing a biosimilar MAA in the EU and is usually not recommended (in accordance with EMA/CHMP/BMWP/403543/2010). Therefore, the *in vivo* data were assessed as complementary information.

2.2.2. Pharmacology

2.2.2.1. Primary pharmacodynamic studies

In order to demonstrate similarity to the reference product, the applicant performed several *in vitro* studies as part of the quality evaluation. From a nonclinical perspective, the results obtained showed no significant differences between Steqeyma and EU-Stelara. The assessment of biosimilarity was primarily based on the quality assessment of the appropriateness and acceptability of the *in vitro* comparability studies conducted.

2.2.2.2. Secondary pharmacodynamic studies

No secondary PD studies were conducted and are not required.

2.2.2.3. Safety pharmacology programme

Safety pharmacology studies are not required for an application under Article 10(4) of Directive 2001/83/EC and in accordance with the applicable EMA/CHMP/BMWP/403543/2010 guideline. However, safety pharmacology parameters were assessed in the *in vivo* 4-week repeat-dose toxicity study in cynomolgus monkeys. Neither Steqeyma nor EU-Stelara showed any adverse effects regarding safety pharmacology parameters. This is in line with the previous data for EU-Stelara (EMA/CHMP/29255/2009).

2.2.2.4. Pharmacodynamic drug interactions

No PD drug interactions studies were conducted and are not required.

2.2.3. Pharmacokinetics

The ELISA method for the quantification of ustekinumab in cynomolgus monkey serum was sufficiently validated. Validation of the bioanalytical ELISA method was conducted in compliance with GLP. Inter- and intra-assay precision and accuracy were acceptable. The comparative TK study was performed as part of an *in vivo* 4-week repeat-dose toxicity study using 45 mg/kg of Steqeyma and EU-Stelara in cynomolgus monkeys. The nonclinical PK studies are considered adequate.

There were no distribution, metabolism, excretion or PK drug interaction studies conducted as part of this application, and none are required in line for a biosimilar development (Article 10(4) of Directive 2001/83/EC and EMEA/CHMP/BMWP/42832/2005 Rev. 1 guideline).

2.2.4. Toxicology

2.2.4.1. Single dose toxicity

No single dose toxicity studies were conducted and are not required (in line with the applicable guideline (EMA/CHMP/BMWP/42832/2005 Rev1)).

2.2.4.2. Repeat dose toxicity

A GLP-compliant, 4-week repeat-dose toxicology study (no 8416958) in cynomolgus monkeys was performed to compare toxicity and toxicokinetics of Steqeyma with EU-Stelara.

Male and female monkeys were administered vehicle control article or 45 mg/kg/dose test article (Steqeyma) or comparative article (EU-Stelara) once weekly via subcutaneous (SC) injection.

There were no notable toxicological differences between Steqeyma and EU-Stelara, and therefore, it is considered that the observations for Steqeyma and EU-Stelara were similar and did not result in any changes of toxicological importance at dose levels up to 45 mg/kg/day and thus, the no observed adverse effect level (NOAEL) was determined to be 45 mg/kg/dose of EU-Stelara or Steqeyma.

2.2.4.3. Genotoxicity

No genotoxicity or mutagenicity studies were performed and are not required (see guideline ICH S6 (R1)).

2.2.4.4. Carcinogenicity

No carcinogenicity studies were performed and are not required (see EMA/CHMP/BMWP/42832/2005 Rev1 and ICH S6 (R1)).

2.2.4.5. Reproductive and developmental toxicity

No reproductive and developmental studies were performed and are not required (see EMA/CHMP/BMWP/42832/2005 Rev1).

2.2.4.6. Toxicokinetic data

The objective of this assessment was to determine the systemic exposure of Steqeyma and EU-Stelara in male and female cynomolgus monkeys after once a week subcutaneous (SC) dosing (45 mg/kg/day) for 4 weeks. Mean concentrations of EU-Stelara or Steqeyma were generally similar and were higher after multiple doses of EU-Stelara or Steqeyma when compared to a single dose. Estimation of elimination phase half-life ($t_{1/2}$) was not attempted for any animals. Non-clinical PK studies do not suggest a significant difference between Steqeyma and the reference product, EU-Stelara.

2.2.4.7. Local Tolerance

Macroscopic observation and histopathological assessments of local (injection site) tolerance were performed in the repeat-dose toxicity study. There were no toxicologically significant differences in injection site findings between control animals and the animals administered Steqeyma or EU-Stelara.

2.2.4.8. Other toxicity studies

No other toxicity studies were performed and are not required.

2.2.5. Ecotoxicity/environmental risk assessment

Steqeyma is a monoclonal antibody and is classified as a protein. Therefore, an environmental risk assessment (ERA) is not required for this medicinal product in accordance with Article 8(3) of Directive 2001/83/EC and the guideline (EMA/CHMP/SWP/4447/00).

2.2.6. Discussion on non-clinical aspects

An abridged nonclinical package was provided to support the MAA for Steqeyma. This is acceptable considering the product is a biosimilar of Stelara for which there is extensive clinical experience. Furthermore, this is in line with the EMA Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). The non-clinical programme was agreed during CHMP scientific advice (EMA/CHMP/SAWP/653523/2019).

In vitro comparability studies (discussed as part of the quality evaluation) did not show significant differences between Steqeyma and EU-Stelara.

As outlined in the CHMP scientific advice (EMA/CHMP/SAWP/653523/2019), the conduct of the *in vivo* 4-week repeat-dose toxicology study with TK assessment in cynomolgus monkeys to compare Steqeyma with EU-Stelara is not required for filing a biosimilar MAA in the EU. Even though it is acknowledged that a repeated dose toxicity study in cynomolgus monkeys may be necessary to gain regulatory approval in other regions, the inclusion of a separate EU-Stelara group in this study was not recommended.

Despite the advice, the applicant completed a 4-week study in cynomolgus monkeys with once weekly dosing via subcutaneous injection comparing 45 mg/kg of Steqeyma to the EU-authorised formulation of EU-Stelara at the same dose levels. Overall, the toxicity profile was comparable between both products for the parameters evaluated during the study.

The nonclinical package is adequate to support biosimilarity against EU Stelara from a non-clinical perspective. Sections 4.6 and 5.3 of the SmPC are in line with the innovator product.

The applicant's justification for the lack of an ERA is acceptable to the CHMP. 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, Steqeyma is not expected to pose a risk to the environment. This is in line with the Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/4447/00 corr 2).

2.2.7. Conclusion on the non-clinical aspects

The design of the non-clinical development programme is appropriate for a biosimilar marketing authorisation application and in line with the relevant guidelines.

In vitro comparability studies (discussed as part of the quality evaluation) did not show significant differences between Steqeyma and EU-Stelara. The toxicity profile of Steqeyma and EU-Stelara assessed in the 4-week study in cynomolgus monkeys was comparable.

The sections 4.6 and 5.3 of the SmPC are in line with the EU reference medicinal product Stelara.

Overall, the non-clinical data is adequate to support biosimilarity of Steqeyma versus the EU reference product Stelara.

2.3. Clinical aspects

2.3.1. 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**

Table 2. Overview of the clinical development plan

Study	Design	Objectives and Endpoints	Treatment	Status	Results
CT-P43 1.1 (comparative PK study)	Phase 1, randomised, double-blind, 3-arm, parallel group, single dose study to compare the PK and safety of three formulations of ustekinumab (CT-P43, EU-Stelara and US-Stelara) in healthy male subjects	Primary: To demonstrate PK similarity in terms of AUC_{0-inf} and C_{max} of CT-P43, EU-Stelara and US-Stelara in healthy male subjects up to Day 127 (Week 18) Secondary: <u>Part 1</u> - To evaluate safety in terms of TEAEs of CT-P43 compared with that of EU-Stelara in healthy male subjects up to Day 29 (Week 4) - To assess PK, additional safety and immunogenicity of CT-P43 and EU-Stelara in healthy male subjects up to Day 29 (Week 4) <u>Both Part 1 and Part 2</u> - To assess additional PK, safety and immunogenicity of CT-P43, EU-Stelara and US-Stelara in healthy male subjects up to Day 127 (Week 18)	45 mg (45 mg/0.5 ml), a single PFS SC injection of study drug [Part 1] Randomised: 30 • CT-P43: 14 • EU-Stelara: 16 [Part 2] Randomised: 241 • CT-P43: 80 • EU-Stelara: 82 • US-Stelara: 79	Completed	Pharmacology • PK • Immunogenicity
					Safety
CT-P43 1.2 (comparative PK study)	Phase 1, randomised, double-blind, 3-arm, parallel group, single dose study to compare the PK and safety of	Primary: To demonstrate PK similarity in terms of AUC_{0-inf} and C_{max} of CT-P43, EU-Stelara and US-Stelara in healthy Japanese male subjects up to Day 113 (Week 16) Secondary: To assess PK,	45 mg (45 mg/0.5 ml), a single PFS SC injection of study drug Randomised: 331 • CT-P43: 114 • EU-Stelara: 110	Completed	Pharmacology • PK • Immunogenicity
					Safety

Study	Design	Objectives and Endpoints	Treatment	Status	Results
	three formulation of ustekinumab (CT-P43, EU-Stelara and US-Stelara) in healthy Japanese male subjects	safety and immunogenicity of CT-P43, EU Stelara and US-Stelara in healthy Japanese male subjects up to Day 113 (Week 16)	· US-Stelara: 107		
CT-P43 3.1 (Comparative efficacy and safety study)	Phase 3, double-blind, randomised, active controlled, parallel group study to compare efficacy and safety of CT-P43 and EU-Stelara in patients with moderate to severe Ps	Primary: To demonstrate CT-P43 is equivalent to EU-Stelara in terms of efficacy as determined by the mean percent improvement from baselines in Psoriasis Area and Severity Index (PASI) score at Week 12. Secondary: To evaluate efficacy, PK, quality of life (QoL), and overall safety including immunogenicity up to Week 52	· Patients who weigh ≤100 kg: 45 mg (1 injection of 45 mg/0.5 ml) of study drug by SC injection via PFS · Patients who weigh >100 kg: 90 mg (2 injections of 45 mg/0.5 ml) of study drug by SC injection via PFS Patients will receive an initial dose of study drug 45 or 90 mg administered subcutaneously, followed by another dose 4 weeks later, and then every 12 weeks thereafter up to Week 40. 1 st Randomized: 509 · CT-P43: 256 · EU-Stelara: 253	Completed	Pharmacology · PK · Immunogenicity
					Efficacy
					Safety

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-inf}, time zero to infinity; C_{max}, maximum serum concentration; CSR, clinical study report; PASI, Psoriasis Area and Severity Index; PFS, pre-filled syringe with safety guard; QoL, quality of life; TEAE, Treatment-emergent adverse event

2.3.2. Clinical pharmacology

2.3.2.1. Pharmacokinetics

Bioanalytical methods

The analytical methods applied during the clinical development include methods for measuring human serum levels of ustekinumab and detecting anti-drug antibodies (ADAs) and neutralising antibodies (NABs) against ustekinumab. The methods (using MSD-ECL and MSD-ECL with SPEAD) have been validated in accordance with relevant FDA guidance, the EMA guidelines on bioanalytical method validation (EMA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2), immunogenicity assessment of therapeutic proteins (EMA/CHMP/BMWP/14327/2006 Rev 1) and immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010). For the ADA and NAB assays, the statistical analysis methods used to determine the cut point are consistent with the procedures recommended by Devanarayan, 2017 and Shankar, 2008.

Bioequivalence

Study CT-P43 1.1

Methods

Study CT-P43 1.1 was a Phase 1, 2-part, randomised, double-blind, 3-arm, parallel group, single dose study to compare the PK and safety of three formulations of ustekinumab (CT-P43, EU-Stelara and US-Stelara), in healthy male subjects.

This study was planned to be conducted in two parts in 270 subjects. The first 30 subjects were enrolled in Part 1 to compare initial safety and 240 subjects were enrolled in Part 2 to demonstrate PK similarity. In part 2, subjects were randomised in a 1:1:1 ratio to receive a single dose (45 mg/0.5 mL) of CT-P43, EU-approved Stelara, or US-licensed Stelara. A study drug (CT-P43, EU-approved Stelara, or US-licensed Stelara) was administered subcutaneously via pre-filled syringe (PFS) on Day 1 and subjects were followed up for 127 days for PK, safety, and immunogenicity assessments.

Primary objective (Part 2):

To demonstrate pharmacokinetic (PK) similarity in terms of area under the concentration-time curve from time zero to infinity (AUC_{0-inf}) and maximum serum concentration (C_{max}) of CT-P43, EU-approved Stelara, and US-licensed Stelara (CT-P43 to EU-approved Stelara, CT-P43 to US-licensed Stelara, and EU-approved Stelara to US-licensed Stelara).

Secondary objectives (Part 2):

Secondary objectives comprised additional PK parameters to support similarity, comparison of safety, tolerability and immunogenicity between CT-P43 and the reference products.

Sampling time points

Samples for PK analysis, were obtained at the following time points:

Table 3. Pharmacokinetics sampling time points

PK sampling time points
Day 1 Pre-dose (within 60 minutes prior to administration of the study drug)
Day 1 (12 hours after the administration of the study drug); ± 30 minutes
Day 2 (24 hours after the administration of the study drug); ± 1 hour
Days 3, 4, 5, 6, 7 and 8 (48, 72, 96, 120, 144 and 168 hours, respectively, after the administration of the study drug); ± 2 hours
Days 9, 10, 11, 12, 15, 18 and 22 (192, 216, 240, 264, 336, 408 and 504 hours, respectively, after the administration of the study drug); ± 4 hours
Days 29, 43, 57, 71, 85 and 99 (672, 1008, 1344, 1680, 2016 and 2352 hours, respectively, after the administration of the study drug); ± 1 day
Day 127 (i.e., EOS; 3024 hours, after the administration of the study drug); ± 2 days

Immunogenicity samples were drawn during the same blood draw for PK samples, where possible.

Statistical methods

For the pairwise comparisons of AUC_{0-inf} and C_{max} , the 90% CI for the ratio of the test and reference products were to be contained within the acceptance interval of 80.00% to 125.00% to demonstrate similarity. The statistical analysis of the log-transformed primary endpoints (AUC_{0-inf} and C_{max}) was based on an ANCOVA model with a treatment as a fixed effect and study centre and body weight as

measured on Day -1 as covariates. Back transformation of the LSM, difference in the LSM and 0% CIs provided geometric means, the ratio of geometric means and 90% CIs for these ratios.

Results

A total of 241 subjects were randomly assigned to a treatment group for Part 2 (80 subjects in the CT-P43 treatment group, 82 subjects in the EU-approved Stelara, and 79 subjects in the US-licensed Stelara treatment group). A summary of demographics and baseline characteristics of subjects in Part 2 is presented in Table 4.

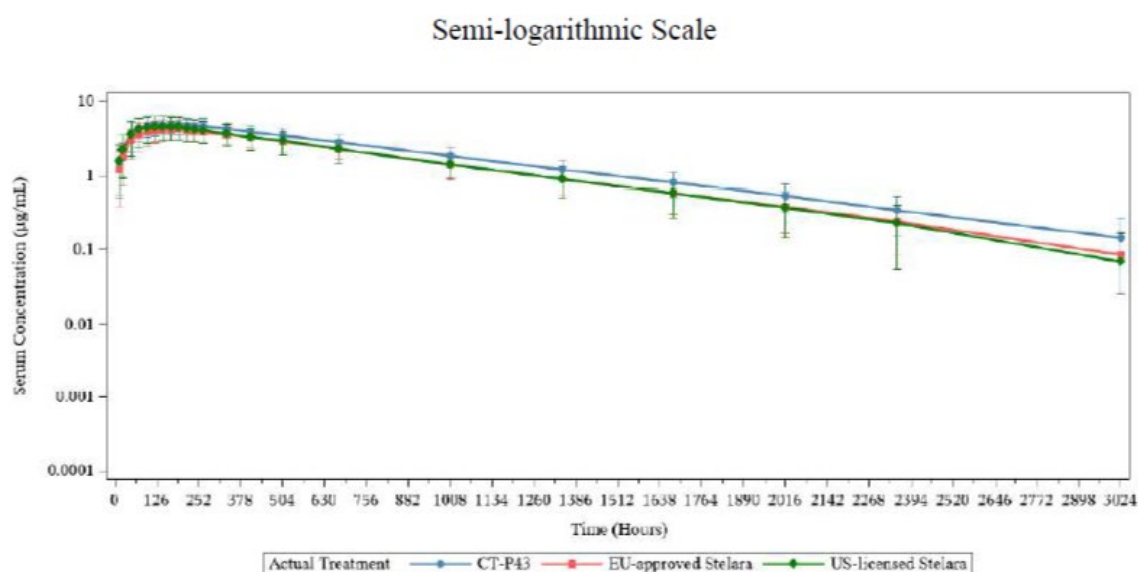
Table 4. Summary of demographics and baseline characteristics – Part 2 (ITT set)

	CT-P43 (N=80)	EU-approved Stelara (N=82)	US-licensed Stelara (N=79)	Total (N=241)
Age (years)				
n	80	82	79	241
Mean (SD)	27.9 (9.21)	30.0 (9.80)	29.2 (9.39)	29.0 (9.48)
Median	25.0	28.0	26.0	26.0
Minimum, Maximum	18, 54	18, 55	18, 54	18, 55
Ethnicity, n (%)				
Hispanic or Latino	3 (3.8)	3 (3.7)	1 (1.3)	7 (2.9)
Non-Hispanic or Non-Latino	72 (90.0)	76 (92.7)	74 (93.7)	222 (92.1)
Unknown	5 (6.3)	3 (3.7)	4 (5.1)	12 (5.0)
Race, n (%)				
American Indian or Alaska native	0	0	1 (1.3)	1 (0.4)
Asian	9 (11.3)	10 (12.2)	14 (17.7)	33 (13.7)
Black or African American	4 (5.0)	3 (3.7)	3 (3.8)	10 (4.1)
Native Hawaiian or Other Pacific Islander	1 (1.3)	1 (1.2)	0	2 (0.8)
White	54 (67.5)	60 (73.2)	54 (68.4)	168 (69.7)
Other	12 (15.0)	8 (9.8)	7 (8.9)	27 (11.2)
Height (cm) at Screening				
n	80	82	79	241
Mean (SD)	178.15 (6.149)	178.03 (7.318)	177.89 (7.556)	178.03 (7.006)
Median	178.50	177.10	178.00	178.00
Minimum, Maximum	164.0, 191.0	162.0, 196.5	158.7, 195.0	158.7, 196.5
Weight (kg) on Day -1				
n	80	82	79	241
Mean (SD)	77.25 (9.699)	78.48 (10.442)	78.10 (10.530)	77.94 (10.202)
Median	75.65	77.00	77.50	76.80
Minimum, Maximum	60.6, 98.2	60.7, 99.4	60.5, 99.8	60.5, 99.8
Weight (Day -1) category, n (%)				
Low ($60 \leq$ to <70)	21 (26.3)	21 (25.6)	21 (26.6)	63 (26.1)
Medium ($70 \leq$ to <80)	27 (33.8)	27 (32.9)	26 (32.9)	80 (33.2)
High ($80 \leq$ to <90)	21 (26.3)	21 (25.6)	21 (26.6)	63 (26.1)

Very High ($90 \leq \text{to} \leq 100$)	11 (13.8)	13 (15.9)	11 (13.9)	35 (14.5)
BMI (kg/m ²) at Screening				
n	80	82	79	241
Mean (SD)	24.308 (3.0529)	24.666 (2.8774)	24.638 (2.8963)	24.538 (2.9351)
Median	24.580	24.600	25.110	24.670
Minimum, Maximum	19.10, 29.95	18.46, 29.94	18.90, 29.78	18.46, 29.95

Abbreviations: BMI, body mass index; EU, European Union; ITT, intent-to-treat; SD, standard deviation; US, United States.

Ustekinumab serum concentrations



Abbreviations: EU, European Unions; PK, pharmacokinetic; SD, standard deviation; US, United States.

Figure 1. Mean ($\pm$ SD) serum concentrations of Ustekinumab by treatment (semi-logarithmic scales) – Part 2 (PK set)

Ustekinumab primary pharmacokinetic parameters

Table 5. Primary pharmacokinetic parameters of Ustekinumab by treatment group – Part 2 (PK set)

	CT-P43 (N=80)	EU-approved Stelara (N=81)	US-licensed Stelara (N=77)
AUC_{0-inf} (day·µg/mL)			
n	79	81	77
Mean (SD)	204.43 (54.513)	162.97 (48.890)	165.86 (61.111)
CV%	26.67	30.00	36.85
Geometric mean	197.07	155.33	154.11
Median	204.78	158.94	157.86
Minimum, Maximum	90.5, 363.6	65.4, 277.8	39.3, 325.3
C_{max} (µg/mL)			
n	80	81	77
Mean (SD)	5.35 (1.456)	4.57 (1.368)	4.86 (1.664)
CV%	27.19	29.93	34.22
Geometric mean	5.16	4.35	4.55
Median	5.15	4.57	4.63
Minimum, Maximum	2.1, 9.6	2.1, 7.6	1.1, 8.3

Abbreviations: AUC_{0-inf}, Area under the concentration-time curve from time zero to infinity; C_{max}, Maximum serum concentration; CV%, percent of coefficient of variation; EU, European Union; PK, pharmacokinetic(s); SD, standard deviation; US, United States.

Statistical analysis of primary PK parameters

Table 6. Statistical Analysis of Primary Serum PK Parameters for Ustekinumab (Analysis of Covariance [ANCOVA]) in Study CT-P43 1.1 Part 2 - PK Set

PK Parameter (unit)	Comparison	Treatment	n	Geometric LS Means ¹	Ratio of Geometric LS Means ¹	90% CI ¹
AUC _{0-inf} (day*µg/mL)	CT-P43	Test	79	193.75	124.36	(115.58, 133.82)
	EU-Stelara	Reference	81	155.79		
	CT-P43	Test	79	193.75	126.40	(117.37, 136.13)
	US-Stelara	Reference	77	153.28		
	EU-Stelara	Test	81	155.79	101.64	(94.42, 109.41)
	US-Stelara	Reference	77	153.28		
C _{max} (µg/mL)	CT-P43	Test	80	5.10	116.18	(108.42, 124.49)
	EU-Stelara	Reference	81	4.39		
	CT-P43	Test	80	5.10	112.02	(104.45, 120.13)
	US-Stelara	Reference	77	4.56		
	EU-Stelara	Test	81	4.39	96.42	(89.92, 103.38)
	US-Stelara	Reference	77	4.56		

Note: The AUC_{0-inf} were not included if adjusted R² < 0.85 for calculating λ_z. An ANCOVA was performed with the natural log-transformed PK parameters as the dependent variable, treatment as a fixed effect and study centre and body weight at Day -1 as covariates.

¹ The LS mean differences and 90% confidence intervals for the differences were exponentiated to provide estimates of the ratio of geometric LS means (CT-P43/EU-Stelara, CT-P43/US-Stelara, and EU-Stelara/US-Stelara) and 90% CIs for the ratios

Abbreviation: n, The number of subjects with non-zero PK parameter values.

The 90% CIs for the geometric LS means ratios of CT-P43 to EU-Stelara, CT-P43 to US-Stelara, and EU-Stelara to US-Stelara in C_{max} were within the pre-defined equivalence margin of 80% to 125%. However, for AUC_{0-inf}, the upper limit of the 90% CIs of the geometric LS means ratio of CT-P43 to EU-Stelara and that of CT-P43 to US-Stelara were above 125% (AUC_{0-inf} (115.58 – 133.82)).

The applicant undertook investigations to understand the observed PK difference in more detail and to see whether any quality- or subject-related factors might have been contributing to this observation. The final conclusions of the applicant following their root-cause analysis were that there were three main factors which contributed to the differences in exposure that were seen in this study; differences in protein content between the test and reference products, differences in the immunogenicity between the test and reference products and a higher clearance and intersubject variability seen patients in the EU-Stelara arm that had a body weight >90 Kg, than that seen in similar patients taking CT-P43.

Protein content

It was found that the clinical batches of CT-P43 used in the study had a higher protein content than EU-Stelara batches, which contributed to the higher serum concentrations observed in the CT-P43 treatment group. Three batches of CT-P43 and one batch of EU-Stelara were used. CT-P43 lots had up to +6.1% higher protein content compared to the EU-Stelara (mean difference: +4.0%). Protein content is a well-known factor affecting PK.

For post-hoc analysis to investigate impact of protein content imbalance on PK results in Study CT-P43 1.1 Part 2, PK parameters were derived using protein content adjusted concentrations for individual subjects as follows:

Protein content-adjusted PK concentration = original PK concentration $\times$ (45 mg / protein content [mg]).

Here, protein content was defined as mean measurement of representative syringes for each batch used in Study CT-P43 1.1 Part 2, multiplying the measured extractable volume and protein concentration.

With the above adjustment, the post-hoc analysis of covariance (ANCOVA) showed that the geometric mean ratio and its upper bound of the 90% confidence intervals (CIs) for AUC_{0-inf} for the pairwise comparison of CT-P43 and EU-Stelara were about 5% points lowered, with the upper bound being closer to the upper limit of bioequivalence criteria (125%) compared to the protein content-unadjusted (original) results in PK set.

Immunogenicity

Immunogenicity is another factor known to impact on PK with the development of anti-drug antibody (ADA) being associated with reduced or undetectable serum ustekinumab concentrations.

In Study CT-P43 1.1 Part 2, a lower proportion of subjects with at least 1 ADA positivity was observed with CT-P43, compared to EU-Stelara: 13 (16.3%) and 24 (29.3%) subjects in the CT-P43 and EU-Stelara groups, respectively.

An ANCOVA analysis showed that for the ADA negative subgroup, the geometric mean ratio and its upper bound of the 90% CIs for AUC_{0-inf} were closer to 125% compared to the original analysis. Compared to the effect of other potential factors on the AUC_{0-inf} point estimate; the effect of immunogenicity alone was modest. The numerically lower immunogenicity with CT-P43 compared to EU-Stelara did not preclude the demonstration of bioequivalence in the second study (Study CT-P43 1.2). It is worth considering that immunogenicity has no impact on C_{max} because ADAs against immunoglobulin G (IgG) monoclonal antibodies are typically formed approximately 3 to 6 weeks after the first dose.

Variability in exposure at higher body weights

Body weight is known as one of the main intrinsic factors affecting ustekinumab PK. To assess the impact of body weight on clearance, the applicant compared the clearance parameters amongst different body weight bands.

The analysis revealed 2 notable characteristics of the dataset. Firstly, as expected, CL/F increases with body weight. Secondly, rather unexpectedly, CL/F and its variability were higher in the EU-Stelara group in comparison to the CT-P43 group in Study CT-P43 1.1 Part 2, especially in subjects over 90 kg. The CL/F observed in the CT-P43 group generally aligns with the historical data of ustekinumab, which showed a moderate increase with body weight, whereas this is not the case in the EU-Stelara group, which has an exaggerated increase in CL/F with body weight. Mean CL/F was approximately 45% and 87% higher in the 90 to 100 kg subgroup compared to the subjects of 60 to 70 kg in the CT-P43 and EU-Stelara groups, respectively (mean [SD]; 301.7 [80.19] and 207.7 [40.28] mL/day in CT-P43 group, and 454.3 [115.16] and 243.3 [38.93] mL/day in EU-Stelara group) in CT-P43 1.1 Part 2.

Demographics and baseline characteristics that might be influential on PK, immunogenicity assay results and individual PK parameters for subjects with a body weight of >90 kg in both groups were also presented. There were no notable trends observed among these subjects that could explain the higher clearance and lower AUC_{0-inf} and C_{max} in subjects having body weights >90 kg in the EU-

Stelara group. As such and given the absence of any difference in quality and CMC that might explain a difference in exposure in higher weight subjects, it can be concluded that differences in outcomes between groups in subjects >90 kg, reflect a play of chance in the randomisation rather than a true difference between CT-P43 and EU-Stelara.

Post-hoc analysis for Study CT-P43 1.1 Part 2

Taking into account the 3 factors of protein content, ADA positivity and variability in exposure at higher body weights, which affect PK, a post-hoc analysis was conducted by the applicant by adjusting protein content, ADA negative subgroup and subjects weighing between 60 to 90 kg, to evaluate the impact of these factors individually and collectively. When each factor is applied individually, the post-hoc analysis showed that the point estimates, along with the lower and upper bounds of the 90% CIs for AUC_{0-inf} were lowered compared to the original analysis. This suggests that all 3 of these factors had an influence on PK, as identified in the population PK modelling and were concurrently applied resulting in a notable shift of PK parameters to within the BE range. The geometric mean ratio and its upper bound of the 90% CIs for AUC_{0-inf} were >10% points lowered with the upper bound being within the upper limit of bioequivalence criteria (125%) compared to the original result.

Table 7. Statistical analysis of primary serum pharmacokinetic parameters (us-excluded ancova) adjusting major factors in study ct-p43 1.1 part 2 (pk set)

	Treatment	AUC_{0-inf} (day* μ g/mL)			C_{max} (μ g/mL)		
		n	Ratio ¹	90% CI ¹	n	Ratio ¹	90% CI ¹
Original (unadjusted)	CT-P43	79	124.59	(116.71,133.01)	80	116.50	(109.05,124.46)
	EU-Stelara	81			81		
Protein Content Adjusted	CT-P43	79	119.86	(112.28,127.95)	80	112.06	(104.96,119.64)
	EU-Stelara	81			81		
ADA Negative Subgroup	CT-P43	66	123.55	(115.61,132.02)	67	118.85	(110.42,127.91)
	EU-Stelara	57			57		
Body Weight 60 to 90 kg	CT-P43	68	120.32	(112.26,128.96)	69	111.90	(104.14,120.24)
	EU-Stelara	69			69		
Protein Content Adjusted & ADA Negative Subgroup	CT-P43	66	119.08	(111.41,127.26)	67	114.53	(106.46,123.21)
	EU-Stelara	57			57		
Protein Content Adjusted & Body Weight 60 to 90 kg	CT-P43	68	115.82	(108.09,124.11)	69	107.70	(100.32,115.63)
	EU-Stelara	69			69		
Protein Content Adjusted & ADA Negative Subgroup & Body Weight 60 to 90 kg	CT-P43	58	114.32	(106.51,122.71)	59	111.37	(103.03,120.37)
	EU-Stelara	49			49		

Sources:

Note: The AUC_{0-inf} were not included if adjusted $R^2 < 0.85$ for calculating λ_z . An analysis of covariance (ANCOVA) was performed with the natural log-transformed PK parameters as the dependent variable, treatment as a fixed effect and study center and body weight as covariates.

¹ The least squares mean differences and 90% confidence intervals for the differences were exponentiated to provide estimates of the ratio of geometric least square means (only CT-P43/EU-Stelara) and 90% CIs for the ratios.

Ustekinumab secondary pharmacokinetic parameters

Median T_{max} occurred at 7.00, 7.03 and 6.00 days and mean $t_{1/2}$ was 22.71, 20.85 and 20.05 days in the CT-P43, EU-approved Stelara, and US-licensed Stelara treatment groups, respectively. Apparent total clearance after subcutaneous dosing (CL/F) and apparent volume of distribution (V_z/F) were generally lower for CT-P43 than EU-approved Stelara or US-licensed Stelara.

Table 8. Secondary pharmacokinetic parameters of ustekinumab – part 2 (pk set)

Parameter (unit)	CT-P43 (N=80)	EU-approved Stelara (N=81)	US-licensed Stelara (N=77)
T_{max} (day)			
n	80	81	77
Mean (SD)	7.19 (2.815)	7.57 (2.538)	6.93 (3.228)
CV%	39.15	33.54	46.54
Geometric mean	6.61	7.12	6.29
Median	7.00	7.03	6.00
Minimum, Maximum	2.0, 14.1	2.9, 14.0	2.0, 21.0
%AUC_{extrap} (%)			
n	79	81	77
Mean (SD)	3.46 (3.370)	3.53 (3.676)	3.54 (3.325)
CV%	97.54	104.18	94.00
Geometric mean	2.84	2.95	2.92
Median	2.78	2.80	2.77
Minimum, Maximum	1.1, 27.7	1.3, 30.9	1.0, 27.4
pAUC_{0-204hr} (day·µg/mL)			
n	80	81	77
Mean (SD)	34.79 (10.718)	29.03 (10.066)	32.40 (12.507)
CV%	30.80	34.67	38.60
Geometric mean	33.10	27.10	29.57
Median	35.08	29.00	29.34
Minimum, Maximum	13.2, 66.0	9.7, 49.2	3.1, 60.5
pAUC_{0-336hr} (day·µg/mL)			
n	80	81	77
Mean (SD)	59.91 (16.257)	50.22 (15.413)	54.42 (19.444)
CV%	27.13	30.69	35.73
Geometric mean	57.64	47.65	50.52
Median	60.50	49.19	50.79
Minimum, Maximum	24.5, 104.1	20.8, 83.0	7.8, 98.5
pAUC_{0-1008hr} (day·µg/mL)			
n	80	81	77
Mean (SD)	141.07 (33.205)	116.65 (31.337)	121.32 (40.584)
CV%	23.54	26.86	33.45
Geometric mean	137.07	112.30	114.03
Median	139.38	114.92	119.21
Minimum, Maximum	63.8, 227.3	57.0, 195.2	34.0, 207.7
pAUC_{1008hr-last} (day·µg/mL)			
n	80	81	77
Mean (SD)	57.89 (21.177)	42.82 (19.130)	41.35 (20.782)
CV%	36.58	44.67	50.25
Geometric mean	53.42	37.96	34.10
Median	55.28	40.62	36.95
Minimum, Maximum	4.6, 118.6	5.4, 88.6	0.1, 110.4
AUC_{0-last} (day·µg/mL)			
n	80	81	77
Mean (SD)	195.76 (52.828)	157.37 (48.051)	160.32 (59.760)
CV%	26.99	30.53	37.28
Geometric mean	188.29	149.72	148.56
Median	197.06	155.33	154.33
Minimum, Maximum	85.0, 346.0	61.9, 271.8	38.5, 298.3
t_{1/2} (day)			
n	79	81	77
Mean (SD)	22.71 (4.532)	20.85 (4.242)	20.05 (4.650)
CV%	19.95	20.35	23.18
Geometric mean	22.22	20.41	19.44
Median	22.62	20.81	20.23
Minimum, Maximum	7.9, 32.5	11.7, 35.6	5.2, 36.5
λ_z (1/day)			
n	79	81	77
Mean (SD)	0.0320 (0.00863)	0.0347 (0.00762)	0.0372 (0.01414)
CV%	26.9453	21.9437	37.9776
Geometric mean	0.0312	0.0340	0.0357
Median	0.0306	0.0333	0.0343
Minimum, Maximum	0.021, 0.088	0.019, 0.059	0.019, 0.133
CL/F (mL/day)			

Pharmacokinetics of Ustekinumab by Anti-Drug Antibody Status

Primary PK parameter AUC_{0-inf} was generally lower in subjects with positive ADA status compared with those subjects with negative ADA status among the 3 treatment groups in the PK Set. Impact of ADA positivity on C_{max} was not found.

Please see below section “Impact of immunogenicity on PK” for further details on immunogenicity.

Study CT-P43 1.2

Methods

Study CT-P43 1.2 was a Phase I, Randomised, Double-Blind, Parallel Group, Single-Dose Study to Compare the Pharmacokinetics, Safety, and Immunogenicity of Three Subcutaneous Injection Formulations of Ustekinumab (CT-P43, EU-approved Stelara, and US-licensed Stelara) in Healthy Japanese Male Subjects.

The study was planned to be conducted in 327 subjects. The 327 subjects were to be enrolled to demonstrate PK similarity and randomised in a 1:1:1 ratio to receive a single dose (45 mg/0.5 mL) of CT-P43, EU-approved Stelara or US-licensed Stelara. All subjects received a single dose of study drug subcutaneously via PFS on Day 1 and were followed up for 113 days for PK, safety and immunogenicity assessments. Subjects were stratified by study centre and body weight at Day -1 (low: 50 to <60 kg; medium: 60 to <70 kg; high: 70 to <80 kg; and very high: 80 to 90 kg, 90 inclusive) to allow for balanced weight distribution.

Primary Objective:

The primary objective of the study was to demonstrate PK similarity of CT-P43 to both EU-Stelara and US-Stelara; as well as to demonstrate similarity between EU-Stelara and US-Stelara, in terms of C_{max} and AUC_{0-inf}. For an EU MA, the comparison between CT-P43 and EU-Stelara is key, while other comparisons are considered supportive.

Secondary Objectives:

Secondary objectives comprised additional PK parameters to support similarity, comparison of safety, tolerability and immunogenicity between CT-P43 and the reference products.

Sampling time points

Samples for PK analysis were obtained at the following time points:

Table 9. Pharmacokinetics sampling time points

PK sampling time points
Day 1 Pre-dose (within 60 minutes prior to administration of the study drug)
Day 1 (12 hours after the administration of the study drug); ±30 minutes
Day 2 (24 hours after the administration of the study drug); ±1 hour
Days 3, 4, 5, 6, 7 and 8 (48, 72, 96, 120, 144 and 168 hours, respectively, after the administration of the study drug); ±2 hours
Days 9, 10, 11, 12, 15, 18 and 22 (192, 216, 240, 264, 336, 408 and 504 hours, respectively, after the administration of the study drug); ±4 hours

Days 29, 43 and 57 (672, 1008, and 1344 hours, respectively, after the administration of the study drug); ± 1 day
Days 71, 85 and 99 (1680, 2016 and 2352 hours, respectively, after the administration of the study drug); ± 2 day
Day 113 (i.e., EOS; 2688 hours, after the administration of the study drug); ± 2 days

Immunogenicity samples were drawn during the same blood draw for PK samples, where possible.

Statistical methods

For the pairwise comparisons of AUC_{0-inf} and C_{max} , the 90% CI for the ratio of the test and reference products were to be contained within the acceptance interval of 80.00% to 125.00% to demonstrate similarity. The statistical analysis of the log-transformed primary endpoints (AUC_{0-inf} and C_{max}) was based on an ANCOVA model with a treatment as a fixed effect and study centre and body weight as measured on Day -1 as covariates. Back transformation of the LSM, difference in the LSM and 0% CIs provided geometric means, the ratio of geometric means and 90% CIs for these ratios.

Results

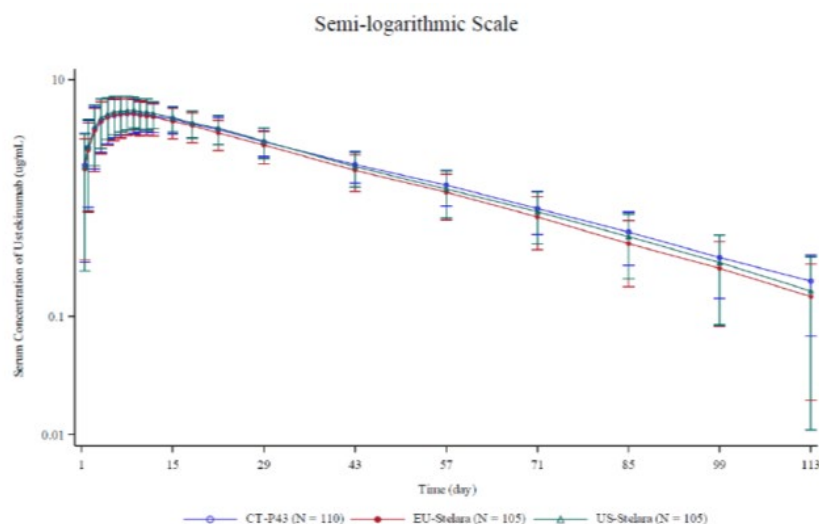
A total of 325 (98.2%) subjects were administered study drug (111 [97.4%] subjects in the CT-P43 treatment arm, 108 [98.2%] subjects in the EU- approved Stelara treatment arm, and 106 [99.1%] subjects in the US-licensed Stelara treatment arm), and 317 (95.8%) subjects in total completed the study (109 [95.6%] subjects in the CT- P43 treatment arm, 105 [95.5%] subjects in the EU-approved Stelara treatment arm, and 103 [96.3%] subjects in the US-licensed Stelara treatment arm). A summary of demographics and baseline characteristics of subjects in Part 2 is presented in Table 10.

Table 10. Summary of demographics and baseline characteristics (ITT set)

	CT-P43 (N=114)	EU-approved Stelara (N=110)	US-licensed Stelara (N=107)	Total (N=331)
Age (years)				
n	114	110	107	331
Mean (SD)	34.6 (10.26)	33.5 (10.52)	36.3 (11.23)	34.8 (10.70)
Median	34.0	33.0	36.0	34.0
Minimum, Maximum	18, 55	18, 55	18, 55	18, 55
Ethnicity, n (%)				
Not Hispanic or Latino	114 (100.0)	110 (100.0)	107 (100.0)	331 (100.0)
Race, n (%)				
Asian (Japanese)	114 (100.0)	110 (100.0)	107 (100.0)	331 (100.0)
Height at Screening (cm)				
n	114	110	107	331
Mean (SD)	171.46 (5.481)	171.31 (5.439)	171.33 (5.703)	171.37 (5.523)
Median	171.25	171.45	172.00	171.50
Minimum, Maximum	160.1, 188.0	157.1, 185.7	157.2, 181.6	157.1, 188.0
Body Weight on Day -1 (kg)				
n	114	110	107	331
Mean (SD)	65.42 (8.454)	66.30 (8.111)	65.24 (8.355)	65.66 (8.297)
Median	65.35	66.00	64.90	65.40
Minimum, Maximum	50.5, 90.0	50.1, 85.5	50.3, 87.0	50.1, 90.0
Body Weight Categories on Day -1, n (%)				
Low: 50 to <60 kg	32 (28.1)	28 (25.5)	31 (29.0)	91 (27.5)
Medium: 60 to <70 kg	48 (42.1)	48 (43.6)	46 (43.0)	142 (42.9)
High: 70 to <80 kg	28 (24.6)	27 (24.5)	26 (24.3)	81 (24.5)
Very high: 80 to 90 kg, 90 inclusive	6 (5.3)	7 (6.4)	4 (3.7)	17 (5.1)
BMI at Screening (kg/m ²)				
n	114	110	107	331
Mean (SD)	22.26 (2.478)	22.57 (2.467)	22.23 (2.621)	22.36 (2.519)
Median	21.90	22.45	22.00	22.00
Minimum, Maximum	18.5, 28.6	18.6, 29.4	18.5, 29.2	18.5, 29.4

Abbreviations: BMI, body mass index; EU, European Union; ITT, intent-to-treat; SD, standard deviation; US, United States.

Ustekinumab serum concentrations



Abbreviations: EU, European Unions; PK, pharmacokinetic; SD, standard deviation; US, United States.

Figure 2. Mean ($\pm$ SD) serum concentrations of ustekinumab by treatment (semi-logarithmic scales) (PK set)

Ustekinumab primary pharmacokinetic parameters

Table 11. Primary pharmacokinetic parameters of ustekinumab by treatment arm (PK set)

	CT-P43 (N=110)	EU-approved Stelara (N=105)	US-licensed Stelara (N=105)
AUC_{0-inf} (day·µg/mL)			
n	109	105	105
Mean (SD)	213.58 (58.896)	197.57 (59.260)	213.44 (61.111)
CV%	27.57	29.99	28.63
Geometric mean	204.89	186.91	204.34
Median	212.28	197.02	213.77
Minimum, Maximum	60.2, 341.5	32.7, 341.9	86.4, 356.9
C_{max} (µg/mL)			
n	110	105	105
Mean (SD)	5.88 (1.902)	5.74 (1.946)	6.19 (1.967)
CV%	32.37	33.90	31.79
Geometric mean	5.56	5.40	5.87
Median	5.68	5.58	5.99
Minimum, Maximum	1.9, 11.0	1.4, 11.1	2.0, 11.5

Abbreviations: AUC_{0-inf}, Area under the concentration-time curve from time zero to infinity; C_{max}, Maximum serum concentration; CV%, percent of coefficient of variation; EU, European Union; PK, pharmacokinetic(s); SD, standard deviation; US, United States.

Statistical Analysis of Pharmacokinetic Similarity

Table 12. Statistical analysis of primary serum pharmacokinetic parameters for ustekinumab (ANCOVA) in Study CT-P43 1.2 - PK Set

PK Parameter (unit)	Comparison	Treatment	n	Geometric LS Means ¹	Ratio of Geometric LS Means ¹	90% CI ¹
AUC _{0-inf} (day·µg/mL)	CT-P43	Test	109	204.22	108.31	(102.07, 114.94)
	EU-Stelara	Reference	105	188.54		
	CT-P43	Test	109	204.22	100.56	(94.76, 106.71)
	US-Stelara	Reference	105	203.09		
	EU-Stelara	Test	105	188.54	92.84	(87.44, 98.57)
	US-Stelara	Reference	105	203.09		
C _{max} (µg/mL)	CT-P43	Test	110	5.43	101.25	(95.14, 107.76)
	EU-Stelara	Reference	105	5.36		
	CT-P43	Test	110	5.43	95.03	(89.29, 101.13)
	US-Stelara	Reference	105	5.71		
	EU-Stelara	Test	105	5.36	93.85	(88.12, 99.96)
	US-Stelara	Reference	105	5.71		

Note: An analysis of covariance (ANCOVA) was performed with the natural log-transformed PK parameters as the dependent variable, treatment as a fixed effect and study centre and body weight at Day -1 as covariates.

¹ The least squares mean differences and 90% confidence intervals for the differences were exponentiated to provide estimates of the ratio of geometric least square means (CT-P43/EU-Stelara, CT-P43/US-Stelara, and EU-Stelara/US-Stelara) and 90% CIs for the ratios

CI: Confidence Interval. LS: Least Squares. n: The number of subjects with non-zero PK parameter values.

Table 13. Statistical analysis of primary serum pharmacokinetic parameters for ustekinumab (ANCOVA) in study CT-P43 1.2 PK set

PK Parameter (unit)	Comparison	Treatment	n	Geometric LS Means ¹	Ratio of Geometric LS Means ¹	90% CI ¹
AUC _{0-inf} (day·µg/mL)	CT-P43	Test	109	204.22	108.31	(102.07, 114.94)
	EU-Stelara	Reference	105	188.54		
	CT-P43	Test	109	204.22	100.56	(94.76, 106.71)
	US-Stelara	Reference	105	203.09		
	EU-Stelara	Test	105	188.54	92.84	(87.44, 98.57)
	US-Stelara	Reference	105	203.09		
C _{max} (µg/mL)	CT-P43	Test	110	5.43	101.25	(95.14, 107.76)
	EU-Stelara	Reference	105	5.36		
	CT-P43	Test	110	5.43	95.03	(89.29, 101.13)
	US-Stelara	Reference	105	5.71		
	EU-Stelara	Test	105	5.36	93.85	(88.12, 99.96)
	US-Stelara	Reference	105	5.71		

Source: [REDACTED]

Note: The AUC_{0-inf} were not included if adjusted R² < 0.85 for calculating λ_z. An ANCOVA was performed with the natural log-transformed PK parameters as the dependent variable, treatment as a fixed effect and study center and body weight at Day -1 as covariates.

¹ The LS mean differences and 90% confidence intervals for the differences were exponentiated to provide estimates of the ratio of geometric LS means (CT-P43/EU-Stelara, CT-P43/US-Stelara, and EU-Stelara/US-Stelara) and 90% CIs for the ratios

Abbreviation: n, The number of subjects with non-zero PK parameter values.

For the primary analysis, in the PK Set, the 90% CIs of the ratio of the geometric means for all PK primary endpoints (C_{max} and AUC_{0-inf}) were entirely contained within the equivalence limits of 80% to 125%, indicating that PK similarity was achieved for CT-P43, EU-approved Stelara and US-licensed Stelara.

Secondary Pharmacokinetic parameter analysis

Table 14. Secondary pharmacokinetic parameters of ustekinumab (PK set)

Parameter (unit)	CT-P43 (N=110)	EU-approved Stelara (N=105)	US-licensed Stelara (N=105)
T_{max} (day)			
n	110	105	105
Mean (SD)	8.14 (3.208)	8.20 (3.717)	7.96 (3.411)
CV%	39.38	45.33	42.85
Geometric mean	7.42	7.35	7.19
Median	8.00	7.98	7.99
Minimum, Maximum	1.0, 17.0	1.0, 21.0	1.0, 21.0
$t_{1/2}$ (day)			
n	109	105	105
Mean (SD)	20.98 (4.669)	19.52 (4.868)	19.88 (5.063)
CV%	22.25	24.94	25.47
Geometric mean	20.45	18.76	19.25
Median	20.79	19.13	19.38
Minimum, Maximum	7.1, 37.9	2.9, 34.7	8.2, 41.5
%AUC _{extrap} (%)			
n	109	105	105
Mean (SD)	3.27 (1.753)	2.97 (1.523)	3.04 (1.895)

CV%	53.53	51.28	62.41
Geometric mean	2.88	2.62	2.59
Median	2.90	2.50	2.60
Minimum, Maximum	0.6, 10.9	0.6, 8.5	0.4, 11.4
pAUC _{0-204hr} (day·µg/mL)			
n	109	105	105
Mean (SD)	36.38 (14.208)	35.99 (14.520)	38.42 (14.367)
CV%	39.06	40.34	37.39
Geometric mean	33.53	32.91	35.55
Median	36.69	34.65	35.82
Minimum, Maximum	9.5, 80.2	5.7, 80.4	8.3, 76.7
AUC _{0-last} (day·µg/mL)			
n	110	105	105
Mean (SD)	204.77 (57.958)	191.58 (56.912)	206.51 (57.541)
CV%	28.30	29.71	27.86
Geometric mean	195.14	181.34	198.10
Median	205.00	189.70	210.80
Minimum, Maximum	36.9, 332.1	31.9, 317.4	83.3, 350.4
λ _z (1/day)			
n	109	105	105
Mean (SD)	0.0349 (0.00963)	0.0396 (0.02309)	0.0373 (0.01056)
CV%	27.5876	58.3755	28.3444
Geometric mean	0.0339	0.0369	0.0360
Median	0.0333	0.0362	0.0358
Minimum, Maximum	0.018, 0.097	0.020, 0.236	0.017, 0.085
CL/F (mL/day)			
n	109	105	105
Mean (SD)	230.62 (82.453)	261.45 (147.859)	231.09 (77.007)
CV%	35.75	56.55	33.32
Geometric mean	219.63	240.76	220.22
Median	211.99	228.41	210.50
Minimum, Maximum	131.8, 748.1	131.6, 1375.8	126.1, 520.8
V _z /F (mL)			
n	109	105	105
Mean (SD)	6732.65 (1949.481)	6891.19 (2540.232)	6362.36 (1848.922)
CV%	28.96	36.86	29.06
Geometric mean	6479.83	6517.49	6117.24
Median	6237.22	6431.27	6082.42
Minimum, Maximum	2257.8, 14199.8	2345.9, 21985.3	2383.3, 14784.5

Abbreviations: %AUC_{extrap}, 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; EU, European Union; CV%, percent of coefficient of variation; pAUC_{0-204hr}, partial area under the concentration-time curve from time zero to 204 hours; 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; V_z/F, apparent volume of distribution during the terminal phase;.

Pharmacokinetic Endpoints of Ustekinumab by Anti- Drug Antibody (ADA) Status

Primary PK parameter AUC_{0-inf} were generally lower in subjects with positive ADA status compared with those subjects with negative ADA status among the 3 treatment arms in the PK Set – ADA negative/positive subset. No apparent correlations were identified between C_{max} and ADA positivity.

The mean secondary AUC parameters were generally lower, while CL/F was higher in subjects with positive ADA status compared with subjects with negative ADA status among the 3 treatment arms in the PK Set – ADA negative/positive subset.

Please see section below on “Impact of immunogenicity on PK” for further details on immunogenicity.

Impact of immunogenicity on pharmacokinetics

As part of the overall investigation of the different findings between the Phase 1 studies, the applicant developed a population PK model, based on data from Studies CT-P43 1.1 and CT P43 1.2, to identify covariates that impact ustekinumab exposure. As well as protein content, immunogenicity was identified as having a significant impact on ustekinumab clearance, which provides support for the applicant’s position that these factors contributed to lack of similarity in AUC (as mentioned in the previous section above).

Study CT-P43 1.1 Part 2

The analyses for maximum serum concentration ($C_{\max}$) and area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) by post-treatment ADA status regardless of pre-dose result are presented for the PK Set in the below Table.

The $AUC_{0-\infty}$ was lower in ADA positive subjects compared to ADA negative subjects in all treatment groups, while there was little impact of ADA positivity on $C_{\max}$.

Table 15. Impact of ADA positivity (post-treatment ADA status regardless of pre-dose result) on $C_{\max}$ and $AUC_{0-\infty}$ in Study CT-P43 1.1 Part 2 (PK Set)

Parameter Statistic	CT-P43 (N=80)		EU-Stelara (N=81)		US-Stelara (N=77)	
	ADA Negative	ADA Positive	ADA Negative	ADA Positive	ADA Negative	ADA Positive
$C_{\max}$ ($\mu\text{g/mL}$)						
n	67	13	57	24	43	34
Mean	5.37	5.29	4.48	4.78	4.85	4.88
Min	2.1	2.5	2.2	2.1	1.1	2.3
Max	9.6	9.5	7.2	7.6	8.3	8.3
$AUC_{0-\infty}$ ($\text{day} \cdot \mu\text{g/mL}$)						
n	66	13	57	24	43	34
Mean	209.70	177.66	167.05	153.27	177.22	151.48
Min	90.5	100.2	84.8	65.4	61.4	39.3
Max	363.6	290.8	256.7	277.8	325.3	287.4

In addition, the post-hoc analyses for $C_{\max}$ and $AUC_{0-\infty}$ by ADA titre separated by ADA high and low, are presented in Table below. Highest post-treatment ADA titres of individual subjects were used in the analyses. Impact of ADA titre on $AUC_{0-\infty}$ was observed while there was no notable impact on $C_{\max}$.

Table 16. Impact of ADA titre on C_{max} in Study CT-P43 1.1 Part 2 (PK Set)

Statistic	CT-P43 (N=80)			EU-Stelara (N=81)			US-Stelara (N=77)		
	Neg	Low	High	Neg	Low	High	Neg	Low	High
n	67	4	9	57	8	16	43	10	24
Mean	5.37	5.52	5.18	4.48	4.85	4.74	4.85	4.49	5.04
Min	2.1	4.2	2.5	2.2	2.1	2.4	1.1	3.1	2.3
Max	9.6	9.5	7.3	7.2	7.6	6.6	8.3	6.0	8.3

Source: [REDACTED]

Note: Post-treatment highest ADA titer value was considered for category. 'Neg' includes the subgroup of ADA negative; 'Low' includes the subgroup of ADA titer low (<30, 30); 'High' includes the subgroup of ADA titer high (90, 270, 810, 2430, 7290).

Table 17. Impact of ADA titre on AUC_{0-inf} in Study CT-P43 1.1 Part 2 (PK Set)

Statistic	CT-P43 (N=80)			EU-Stelara (N=81)			US-Stelara (N=77)		
	Neg	Low	High	Neg	Low	High	Neg	Low	High
n	66	4	9	57	8	16	43	10	24
Mean	209.70	171.50	180.40	167.05	177.23	141.29	177.22	158.76	148.45
Min	90.5	132.1	100.2	84.8	80.3	65.4	61.4	120.1	39.3
Max	363.6	263.2	290.8	256.7	277.8	230.7	325.3	208.2	287.4

Source: [REDACTED]

Note: Post-treatment highest ADA titer value was considered for category. 'Neg' includes the subgroup of ADA negative; 'Low' includes the subgroup of ADA titer low (<30, 30); 'High' includes the subgroup of ADA titer high (90, 270, 810, 2430, 7290). If the adjusted R² < 0.85, AUC_{0-inf} were excluded from the statistical analysis.

Study CT-P43 1.2

The AUC_{0-inf} was lower in ADA positive subjects compared to ADA negative subjects in all treatment groups, while there was little impact of ADA positivity on C_{max}, which is in line with the finding from Study CT-P43 1.1 Part 2.

Table 18. Impact of ADA positivity (post-treatment ADA status regardless of pre-dose result) on C_{max} and AUC_{0-inf} in Study CT-P43 1.2 (PK Set)

Parameter Statistic	CT-P43 (N=110)		EU-Stelara (N=105)		US-Stelara (N=105)	
	ADA Negative	ADA Positive	ADA Negative	ADA Positive	ADA Negative	ADA Positive
C_{max} (µg/mL)						
n	92	18	58	47	63	42
Mean	6.04	5.04	5.55	5.97	6.11	6.30
Min	2.2	1.9	1.4	2.6	2.0	2.4
Max	11.0	9.0	9.5	11.1	9.9	11.5
AUC_{0-inf} (day*µg/mL)						
n	91	18	58	47	63	42
Mean	220.45	178.86	203.02	190.84	221.99	200.63
Min	108.7	60.2	53.1	32.7	102.6	86.4
Max	341.5	306.6	341.9	328.0	356.9	316.2

In addition, the post-hoc analyses for C_{max} and AUC_{0-inf} by ADA titre are presented below. Highest post-treatment ADA titres of individual subjects were used in analysis for C_{max} and AUC_{0-inf} . Impact of ADA titre on AUC_{0-inf} was observed while there was no notable one on C_{max} , the same trend observed in Study CT-P43 1.1 Part 2.

Table 19. Impact of ADA titre on C_{max} in Study CT-P43 1.2 (PK Set)

Statistic	CT-P43 (N=110)			EU-Stelara (N=105)			US-Stelara (N=105)		
	Neg	Low	High	Neg	Low	High	Neg	Low	High
n	92	3	15	58	13	34	63	18	24
Mean	6.04	5.28	4.99	5.55	6.30	5.85	6.11	6.15	6.42
Min	2.2	4.6	1.9	1.4	3.0	2.6	2.0	2.4	3.0
Max	11.0	6.1	9.0	9.5	10.8	11.1	9.9	9.1	11.5

Source: [REDACTED]

Note: Post-treatment highest ADA titer value was considered for category. 'Neg' includes the subgroup of ADA negative; 'Low' includes the subgroup of ADA titer low (<30, 30); 'High' includes the subgroup of ADA titer high (90, 270, 810, 2430, 7290, 21870).

Table 20. Impact of ADA titre on AUC_{0-inf} in Study CT-P43 1.2 (PK Set)

Statistic	CT-P43 (N=110)			EU-Stelara (N=105)			US-Stelara (N=105)		
	Neg	Low	High	Neg	Low	High	Neg	Low	High
n	91	3	15	58	13	34	63	18	24
Mean	220.45	188.21	176.99	203.02	210.22	183.43	221.99	210.03	193.58
Min	108.7	151.7	60.2	53.1	96.8	32.7	102.6	86.4	104.0
Max	341.5	212.3	306.6	341.9	328.0	326.9	356.9	316.2	314.0

Source: [REDACTED]

Note: Post-treatment highest ADA titer value was considered for category. 'Neg' includes the subgroup of ADA negative; 'Low' includes the subgroup of ADA titer low (<30, 30); 'High' includes the subgroup of ADA titer high (90, 270, 810, 2430, 7290, 21870). If the adjusted $R^2 < 0.85$, AUC_{0-inf} were excluded from the statistical analysis.

The applicant was asked to discuss the inconsistency in the proportion of subjects with at least 1 positive ADA result between EU Stelara arms in Study 1.1 and Study 1.2 in terms of proportion of subjects who had at least 1 positive ADA result (29.3% and 44.4%, respectively), resulting in greater differences in immunogenicity seen in Study 1.2 between CT-P43 and EU Stelara. The applicant was also asked to discuss the difference in proportion of subjects who had at least 1 positive NAb result after administration of study drug for CT-P43 and EU Stelara, in Study 1.1. (6.3% and 7.3%) compared to Study 1.2 (12.6% and 16.77%). The applicant reviewed Quality attributes to see if any differences in the quality of EU-Stelara lots used in Studies CT-P43 1.1 Part 2 and CT-P43 1.2 were evident that would be expected to result in higher levels of ADA or NAb in Study CT-P43 1.2. The applicant noted the slightly higher level of sialic acid containing glycans (approximately 3% higher) in the EU-Stelara lot used in Study CT-P43 1.2 compared to the lot used in Study CT-P43 1.1 Part 2, but considered this difference too small to be the reason for the different ADA incidence, and the rationale would not translate to the data seen with US Stelara. Otherwise, no other quality attributes compared between batches were considered relevant for the differences in positive ADA between Study CT-P43 1.1 Part 2 and Study CT-P43 1.2.

On review of clinical aspects, the applicant noted differences between studies in terms of race (mainly White in Study CT-P43 1.1 and Asian in Study CT-P43 1.2) and proportion of immune system disorders

which was higher for all groups ~20-26% in Study CT-P43 1.1 compared to Study CT-P43 1.2 ~4-5%. However, it is not clear that such differences would explain the higher proportion of subjects with positive ADA after administration with EU Stelara in Study CT-P43 1.2 compared to in Study CT-P43 1.1. Also on review of pre-existing ADA levels in each treatment group of both studies, slight differences were observed, (For Study CT-P43 1.1 Part 2, 2.5%, 2.4% and 5.1% in the CT-P43, EU-Stelara and US Stelara groups, respectively; For Study CT-P43 1.2, 3.6%, 0 and 0, respectively), but this was not considered to explain the different post-dose immunogenicity results for EU-Stelara between the studies.

Table 21. Immunogenicity Results for Post-treatment Status (Safety Set)

Study	% (n/N)	CT-P43	EU-Stelara	US-Stelara
CT-P43 1.1 Part 2	At Least One Positive ADA After Administration	16.3% (13/80)	29.3% (24/82)	43.6% (34/78)
	At Least One Positive NAb After Administration	6.3% (5/80)	7.3% (6/82)	11.5% (9/78)
CT-P43 1.2	At Least One Positive ADA After Administration	16.2% (18/111)	44.4% (48/108)	39.6% (42/106)
	At Least One Positive NAb After Administration	12.6% (14/111)	16.7% (18/108)	15.1% (16/106)

Note: N represents the number of subjects in safety set in each treatment group. The NAb assessments were only made on samples with an ADA result of 'Positive'.

Study CT-P43 3.1

The serum concentration for the ADA positive subgroup was slightly lower than that for the ADA negative subgroup in both treatment groups regardless of dose. The serum concentration was generally similar between the two treatment groups however in both ADA positive and negative subgroups.

Table 22. Serum Concentrations of Ustekinumab (µg/mL) by ADA Status in Study CT-P43 3.1 (PK Set)

Visit	Dose	CT-P43 (N=256)				EU-Stelara (N=248)			
		ADA positive		ADA negative		ADA positive		ADA negative	
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Week 4 (Pre-dose)	45 mg	24	2.3 (0.9)	172	2.4 (0.8)	53	2.0 (0.9)	140	2.3 (0.8)
	90 mg	5	2.0 (1.6)	53	3.5 (1.1)	20	2.5 (1.3)	33	2.8 (1.1)
Week 12	45 mg	24	1.1 (0.7)	174	1.4 (0.6)	54	0.8 (0.6)	138	1.3 (0.7)
	90 mg	5	0.8 (0.8)	53	1.9 (0.7)	20	1.2 (0.9)	34	1.4 (0.7)
Week 16 (Pre-dose)	45 mg	24	0.3 (0.3)	171	0.6 (0.3)	53	0.3 (0.3)	139	0.5 (0.4)
	90 mg	5	0.2 (0.3)	53	0.7 (0.3)	20	0.4 (0.4)	34	0.6 (0.4)

Source:

Note: Below lower limit of quantification prior to the first study drug administration (Week 0, Dose 1) was treated as zero (0), and all other BLQ values was also set to zero (0). Samples were collected at pre-dose (prior to the beginning of study drug administration) except Week 12 at which the blood sample was taken at any time.
Abbreviation: SD, standard deviation

In addition, the post-hoc analysis for the serum concentrations by ADA titre at Week 12 is presented in Table below. The results show that the serum concentration tends to be lower in the patients with higher ADA titre in a comparable manner in both dose groups and in both treatment groups.

Table 23. Impact of ADA titre at Week 12 on Serum Concentration (µg/mL) in Study CT-P43 3.1 (PK Set)

Dose Statistic	CT-P43 (N=256)			EU-Stelara (N=248)		
	Neg	Low	High	Neg	Low	High
45 mg						
n	182	7	9	152	9	31
Mean	1.4	1.3	0.7	1.3	0.9	0.6
Min	0.3	0.6	0	0	0.2	0
Max	3.5	2.6	2.1	4.1	2.0	2.6
90 mg						
n	53	2	3	38	7	9
Mean	1.9	1.7	0.3	1.4	1.3	1.0
Min	0.2	1.5	0	0.1	0.3	0
Max	4.1	1.9	0.7	3.1	2.5	3.2

Source: [REDACTED]
Note: 'Neg' includes the subgroup of ADA negative at Week 12; 'Low' includes the subgroup of ADA titer low (<30, 30) at Week 12; 'High' includes the subgroup of ADA titer high (90, 270, 810, 2430, 7290, 21870) at Week 12. Below lower limit of quantification values were set to zero (0). Samples at Week 12 were collected at any time.

Post-Hoc pooled analysis

In order to further support the demonstration of bioequivalence between CT-P43 and EU-Stelara. The applicant conducted a pooled analysis of the PK results of Studies CT-P43.1.1 part 2 and CT-P43 1.2. This analysis was possible as the design and conduct of both studies was sufficiently similar to reduce the risk of significant heterogeneity between the studies, the only significant difference being the product used. As staged above, the applicant specifically chose batches of drug substance and drug product with similar protein content to the commercially available batches of EU-Stelara procured for study CT-P43 1.2, while all other design and analysis aspects remained the same.

The post-hoc analysis of pooled data showed that 90% confidence intervals (CIs) for ratio of geometric least squares (LS) means of AUC_{0-inf} and C_{max} of CT-P43 versus EU-Stelara were all contained within the equivalence margin of 80-125%, (AUC_{0-inf} 109.55, 120.30, C_{max} 102.45, 112.48). The secondary PK endpoints were all comparable.

In addition, the applicant conducted a post-hoc tipping point analysis to test the robustness of the results. This was done by sequentially repeating the analysis while progressively increasing the confidence interval for the geometric mean of the AUC by 0.01% increments until such time that a maximum CI of 99.99% was reached or the results were no longer within the CI. The outcome of this exercise was that the results remained significant up to a CI of 99.89% for the acceptance range of 80.00 to 125.00 for the AUC.

2.3.2.2. Pharmacodynamics

Mechanism of action

Ustekinumab binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Binding of the antigen binding fragment (Fab) domain of ustekinumab to the p40 protein subunit of both IL-12 and IL-23 inhibits the cytokines from binding to IL-12 and IL-23 receptor complexes on the surface of natural killer (NK) cells or T cells, thereby preventing initiation of downstream immune-response signalling pathways.

Primary and Secondary pharmacology

Since this is a biosimilar application, the primary and secondary pharmacology does not have to be characterised.

2.3.3. Discussion on clinical pharmacology

Bioanalytical methods

The analytical methods used during clinical development have been validated in accordance with the EMA guidelines on bioanalytical method validation (EMA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2), immunogenicity assessment of therapeutic proteins (EMA/CHMP/BMWP/14327/2006 Rev 1) and immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use (EMA/CHMP/BMWP/86289/2010). Upon the CHMP's request, the applicant provided long-term stability validation results for CT-P43 in serum, which met the acceptance criteria of the ICH guidance M10 on bioanalytical method validation and study sample analysis (EMA/CHMP/ICH/172948/2019; FDA, 2022). The applicant adequately justified the lack of the evaluation of the interference of the concomitant analyte during validation which was due to the fact that in the two Phase I studies, ustekinumab was administered without any concomitant medicinal product to healthy volunteers, thus the interference of the concomitant analyte was not evaluated during validations. In addition, the data provided showed that there was no interference of serum components in PK evaluation.

Pharmacokinetics

To support the demonstration of biosimilarity of CT-P43 against Stelara, the applicant has submitted the results of two pharmacokinetic studies, supported by the pharmacokinetic results from a comparative efficacy study in patients with moderate to severe psoriasis.

Study CT-P43 1.1 was a randomised, 2-part, double-blind, parallel group, single dose, 3-arm study in healthy subjects to demonstrate similarity in PK, safety, tolerability and immunogenicity between CT-P43, EU-Stelara and US-Stelara.

Overall, the design of the Phase I study CT-P43 1.1 is in accordance with the "Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010). Given the long elimination half-life of ustekinumab (approximately 3 weeks), the parallel design is acceptable. Subjects were randomised in a 1:1:1 ratio to receive either CT-P43, EU-Stelara or US-Stelara. The total study duration was approximately 17 weeks.

Subjects received a single dose of 45 mg of either CT-P43, EU-Stelara, or US-Stelara on Day 1 as a SC injection. This is appropriate and in line with previous experience and advice. The 45 mg dose falls within the linear dose-exposure range (24 – 240 mg, SmPC Stelara) following a single SC administration and it is also the lowest therapeutic dose in patients and expected to induce a higher immunogenicity response compared to the 90 mg dose. As such, 45 mg dose is considered a sufficiently sensitive choice for the demonstration of biosimilarity between CT-P43 and EU-Stelara, and as it represents the lowest therapeutic dose in patients is also a viable option regarding participant's safety. In addition, the SC route is preferable regarding the objective of PK comparability, since it covers both absorption and elimination.

The PK sampling scheme extends out to Day 127. Given that the median half-life ($t_{1/2}$) of ustekinumab was approximately 3 weeks (ranging from 15 to 32 days), the sampling period is considered reasonable for the majority of subjects, and this was confirmed by the acceptable number (%) of subjects with AU extrapolation >20%.

The primary objective of the study was to demonstrate PK similarity of CT-P43 to both EU-Stelara and US-Stelara; as well as to demonstrate similarity between EU-Stelara and US-Stelara, in terms of $C_{\max}$ and $AUC_{0-\infty}$. For an EU MA, the comparison between CT-P43 and EU-Stelara is key. Secondary objectives comprised additional PK parameters to support similarity, comparison of safety, tolerability and immunogenicity between CT-P43 and the reference products.

The primary endpoints were $C_{\max}$ and $AUC_{0-\infty}$. This is in line with relevant EMA guideline for a single dose study with subcutaneous administration. The secondary PK endpoints are acceptable. The assessment of biosimilarity in terms of PK was based on 90% confidence intervals (CIs) for the ratio of the geometric means (CT-P43/EU-Stelara) for $C_{\max}$ and $AUC_{0-\infty}$ of the ustekinumab concentrations which had to be contained within the bioequivalence limits of 80-125%. The equivalence margins used in the study are in line with conventionally used margins for biosimilar products. Study objectives are overall adequate for the purpose of conducting a PK biosimilarity exercise.

The statistical plan and proposed analyses are acceptable. The statistical analysis of the log-transformed primary endpoints ($AUC_{0-\infty}$ and $C_{\max}$) was based on an ANCOVA model with treatment as a fixed effect and study centre and body weight as measured on Day -1 as covariates. Back transformation of the LSM, difference in the LSM and 0% CIs provided geometric means, the ratio of geometric means and 90% CIs for these ratios.

Biosimilarity of CT-P43 compared to EU-Stelara could not be demonstrated for the co-primary endpoint $AUC_{0-\infty}$, as the 90% CI for the geometric mean ratio for $AUC_{0-\infty}$ (115.58 – 133.82) fell outside the acceptance range of 80.00% to 125.00%. In addition, the 90% CIs for $C_{\max}$ were within the acceptance limits (108.4 – 124.49) but did not include unity.

Post-hoc root cause analyses suggested that three main factors, protein content, immunogenicity and increased and variable clearance related with increased bodyweight, played a significant role in this finding, and that repeat analyses controlling for these aspects brought the geometric mean and confidence interval of that mean back within the acceptable range. Taken together, it is agreed that these covariates can explain the differences seen in this study.

Study CT-P43 1.2 was a phase I, randomised, double-blind, parallel group, single-dose study to compare the pharmacokinetics, safety, and immunogenicity of three subcutaneous injection formulations of ustekinumab (CT-P43, EU-approved Stelara, and US-licensed Stelara) in healthy Japanese male subjects. The study was planned to be conducted in 327 subjects. The 327 subjects were to be enrolled to demonstrate PK similarity and randomised in a 1:1:1 ratio to receive a single dose (45 mg/0.5 mL) of CT-P43, EU-approved Stelara or US-licensed Stelara. Subjects received a single dose of 45 mg of either CT-P43, EU-Stelara, or US-Stelara on Day 1 as a SC injection. This is appropriate and in line with previous experience.

The design of the Phase I study CT-P43 1.2 is in accordance with the "Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010). The eligibility criteria are acceptable and in line with previously received advice. In this study, all patients were Japanese, but the applicant clarified that race is not a significant covariate with regards to exposure, and as such the results are considered generalisable.

Following on from the failure to demonstrate bioequivalence in the initial study (CT-P43 1.1), the applicant stated that they specifically chose batches of their product that had similar protein content to both the EU- and US- versions of Stelara. These drug product batches were made from drug substance batches that had been used to make the medicines used in the initial study, and as such the only differences between the medicine used in both studies relate to protein content. In addition, the drug manufacturing process used to make the drug product for CT-P43 1.2 were representative of those

which are intended to be used when making commercial batches of the medicinal product. As such, the drug product used in CT-P43 1.2 are acceptable as being representative.

The primary objective of the study was to demonstrate PK similarity of CT-P43 to both EU-Stelara and US-Stelara in terms of C_{max} and AUC_{0-inf} . The primary endpoints were C_{max} and AUC_{0-inf} . This is in line with relevant EMA guidance for a single dose study with subcutaneous administration. Secondary objectives comprised additional PK parameters to support similarity, comparison of safety, tolerability, and immunogenicity between CT-P43 and the reference products. The secondary PK endpoints are acceptable.

The assessment of biosimilarity in terms of PK was based on 90% confidence intervals (CIs) for the ratio of the geometric means (test/EU-Stelara) for C_{max} and AUC_{0-inf} of the ustekinumab concentrations which had to be contained within the bioequivalence limits of 80-125%. The equivalence margins used in the study are in line with conventionally used margins for biosimilar products. For an EU MA, the comparison between CT-P43 and EU-Stelara is key, while other comparisons are considered supportive.

The sampling timepoints are appropriate for the characterisation of the PK parameters.

The 90% CIs of the ratio of the geometric means for all PK primary endpoints (C_{max} and AUC_{0-inf}) were entirely contained within the equivalence limits of 80% to 125%, with the CI for C_{max} being 95.14 – 107.76, and the CI for AUC_{0-inf} being 102.07 – 114.94. The 90% CI for AUC_{0-inf} for the pairwise comparison of CT-P43 and EU-Stelara did not cross unity (102.07 – 114.94); however, CHMP have concluded that this in itself does not represent a significant finding in this context.

The applicant suggested post-hoc investigation showed that differences in the protein content of the CT-P43 batches used in Study CT-P43 1.1 was the most likely reason for failing to show bioequivalence, and that controlling for this in Study CT-P43 1.2 allowed demonstration of bioequivalence to occur. The fact that the drug manufacturing process used to make the drug product administered in Study CT-P43 1.2 was representative of that which will be used for the manufacturing of commercial batches is acceptable.

The applicant also suggested that the lower immunogenicity of CT-P43 compared with EU-Stelara is another potential factor in the difference in PK that was seen in the studies, and while additional analyses have confirmed that lower immunogenicity does indeed have an impact on the results presented, protein content was the main cause of differences in exposure between CT-P43 and EU Stelara.

The applicant also conducted a pooled analysis of the protein-corrected and protein-unadjusted PK results from both studies, which showed that the totality of the PK data was within the acceptance margins for both C_{max} and AUC. The applicant has also shown that any differences between the trial populations for both studies are not likely to have any significant effect on the reliability of those results, which is acceptable. Further tipping point analyses confirmed the robustness of that result out to a CI of 99.89%, in the pooled analysis performed with protein-corrected and a CI of 99.69% in the pooled analysis performed with protein-unadjusted, in line with the suggestion of the Methodology Working Party (MWP).

Comparability of IV and SC forms

Data regarding the comparability of the IV and SC forms have been presented by the applicant and are discussed in the quality sections of this assessment. In addition, the applicant has performed a comparison of partial AUCs covering the elimination phase between the proposed biosimilar and the originator product for both study CT-P43 1.2 analyses which demonstrated comparability in the absorption and elimination phases for the SC route of administration.

Additional expert consultation

During the procedure, the Methodology Working Party (MWP) was consulted to address questions from CHMP. A summary of the responses is provided below.

- **Failed co-primary endpoint AUC_{0-inf} in study CT-P43 1.1 and differences in the protein content of the Steqeyma, CT-P43 batches used in this study**

MWP commented that the differences in the protein content of the Steqeyma, CT-P43 batches used in Study CT-P43 1.1 is likely a contributing factor, however it seems not plausible that it is the only reason for the observed difference in AUC between CT-P43 and Stelara.

- **Tipping point analysis (in terms of largest coverage probability of the confidence interval within the acceptance range) for the pooled data setting**

MWP commented that the applicant has provided the requested tipping point analysis and seems to have performed them appropriately. It is noted that the most 'extreme' of all the analysis was a 99.69% confidence interval which was observed in the pooled analysis performed with protein-unadjusted (original) PK data. When PK parameters were adjusted with protein content for the pooled analysis, the results show that the 99.89% CI is the largest CI for AUC_{0-inf} that would still be within the acceptance range.

- **Comparison of partial AUCs covering the elimination phase between the proposed biosimilar and the originator product for both studies 1.1 and 1.2, in order to support extrapolation of the SC data to the IV administration route and to waive a clinical study using the IV presentation**

MWP considered these analyses as descriptive rather than pivotal.

- **Role of the apparently/potentially conflicting results of the two studies, taking into consideration changes in the inclusion criteria, sample size and protein content (for biosimilars), to the second study**

It is a matter of clinical judgement whether the results can be combined or not, based on the differences between the trials.

The factors proposed may explain the differences, but the existence of differences may prevent the data from being pooled. In the event it is considered that they cannot be pooled, then it may be most appropriate to rely on the trial that is most relevant to the proposed indicated product, i.e. the second analysis. In this situation, the relevance of the first trial to the decision is questionable. In the event that they can be pooled, as long as the combined analysis yields statistical evidence considerably stronger than $p < 0.05$, it may be acceptable.

2.3.4. Conclusions on clinical pharmacology

Biosimilarity of Steqeyma to EU-Stelara was demonstrated in the second PK study CT-P43 1.2. In addition, a post-hoc pooled analysis, along with a tipping point sensitivity analysis of those results, confirmed that the totality of the PK data indicates the biosimilarity of the test and reference products.

Although biosimilarity could not be demonstrated in the first study CT P-43 1.1, the post-hoc root cause analyses conducted by the applicant confirm that acceptable differences in protein content and in the relative immunogenicity between the test and reference products in the study, along with an increased but probably random variability in the clearance seen in patients with increased bodyweight contributed significantly to this finding.

Bioequivalence of CT-P43 and EU-Stelara has been established.

2.3.5. Clinical efficacy

2.3.5.1. Dose response study(ies)

Not applicable for biosimilars.

2.3.5.2. Main study

Study CT-P43 3.1

Methods

Study CT-P34 3.1 was a randomised, active-controlled, double-blind, multicentre, Phase 3 study designed to evaluate efficacy, PK, quality of life (QoL), and overall safety including immunogenicity and biomarker of CT-P43 compared with EU-Stelara in patients with moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy. Patients received either CT-P43 or EU-Stelara 45 mg (who weighed ≤ 100 kg) or 90 mg (who weighed > 100 kg) administered subcutaneously at Weeks 0, 4, 16, 28, and 40 based on patient's baseline body weight.

The study comprised the following periods:

- Screening Period: Day -42 [up to 6 weeks] to Day -1
- Treatment Period: Week 0 to Week 40
- Treatment Period I (16 weeks)
- Treatment Period II (24 weeks)
- Off-dose follow-up period (12 weeks) prior to the End-of-Study (EOS) visit.
- EOS visit: Week 52

Treatment Period I (from Week 0 to Week 16)

On Day 1 (Week 0), patients who met all the inclusion criteria and none of the exclusion criteria were to be enrolled in the study and randomly assigned to receive either CT-P43 or EU-Stelara prior to treatment using a 1:1 allocation ratio. Patients were to receive CT-P43 or EU-Stelara up to Week 16.

Treatment Period II (after Treatment Period I and prior to follow-up period)

Prior to dosing at Week 16, patients in the EU-Stelara group were to be randomly assigned in a ratio of 1:1 to either continue EU-Stelara or undergo the transition to CT-P43 from Week 16. All patients who were initially randomly assigned to CT-P43 at Day 1 (Week 0) were to continue their treatment with CT-P43 until the end of the study. The second randomisation process was also to be conducted in the CT-P43 group prior to dosing at Week 16 to maintain the study blind.

A schematic diagram for patient assignment in Treatment Period I and Treatment Period II is presented in the study design.

- **Study Participants**

Main inclusion criteria

Each patient had to meet all the following criteria to be enrolled in this study:

1. Patient was male or female aged 18 to 80 years old, both inclusive;
2. Patient had a diagnosis of plaque-type psoriasis for at least 24 weeks before the first administration of the study drug (Day 1);
3. Patient had stable moderate to severe chronic plaque psoriasis as defined;
4. Patient was a candidate for phototherapy or systemic therapy;
5. Patient had adequate renal and hepatic function at Screening as defined;
6. Patient had acceptable haematology laboratory test results at Screening;
7. Patient had to have given written informed consent before participation in the study;
8. Female patient who was considered of childbearing potential had to agree to use highly effective methods of contraception. Male patient also had to agree to use the highly effective method as described.

Main exclusion criteria

1. Patient diagnosed with forms of psoriasis other than plaque-type;
2. Patient previously received ustekinumab or a biosimilar of ustekinumab or any drug that directly targets IL-12 or IL-23;
3. Patient who had prior exposure to 2 or more biologic agents approved for the treatment of psoriasis. Patients with 1 prior biologic could be enrolled after sufficient washout period of 12 weeks or 5 half-lives;
4. Patient who had concurrent or chronic inflammatory or autoimmune disease;
5. Patient who had allergies to the active substance or any of the excipients of any of study drugs;
6. Patient who received a live or live-attenuated vaccine within 4 weeks prior to the first administration of the study drug (Day 1);
7. Patient who had Bacillus Calmette-Guérin (BCG) vaccination within 1 year prior to the first administration of the study drug;
8. Patient who had a concurrent or past history of any significant infection;
9. Patient who had a concurrent or history of a TB condition;
10. Patient who had a significant co-existing medical condition;
11. Patient who received or planned to receive any of the prohibited medications or treatment that could affect psoriasis;
12. Female patient who was currently pregnant or breastfeeding or is planning to become pregnant or breastfeed within 15 weeks of the last dose of study drug;
13. Male patient who planned to donate sperm or father a child within 15 weeks of the last dose of study drug;
14. Patient who was not willing to limit ultraviolet light exposure during the study;

15. Patient who had current active alcohol or drug abuse or history within the previous 1 year from Screening;
16. Patient was vulnerable (as defined);
17. Patient who, in the opinion of the investigator, should not participate in the study.

- **Treatments**

Patients received either CT-P43 or EU-Stelara 45 or 90 mg administered subcutaneously at Weeks 0, 4, 16, 28, and 40 based on patient's baseline body weight. However, in case significant body weight change occurred and resulted in over 10% outside from threshold weight, adjusted dose was to be administered to all treatment groups in Treatment Period II.

Study drug was administered by a predefined unblinded staff at the site during the study. Sites for injection were either the upper thighs, around the abdomen at least 5 cm away from the navel, upper arm, or buttocks. Areas of skin that showed signs of psoriasis were avoided. In the case of the 90 mg dose, 2 injections of 45 mg PFS of study drug were given at 2 different sites for each injection with the second injection given right after the first.

Table 24. Study drugs, dose and mode of administration, and batch numbers

Study Drug	Dose and Mode of Administration	Supplied as	Batch/Lot Numbers (Expiry Date)
CT-P43 (Test Product)	45 mg or 90 mg, SC injection	Pre-filled syringes containing 45 mg/0.5 mL of ustekinumab (CT-P43)	0NGA05 (January 2022) 0NGA06 (April 2022)
EU-Stelara (Reference Product)	45 mg or 90 mg, SC injection	Pre-filled syringes containing 45 mg/0.5 mL of ustekinumab (EU-Stelara)	JHS1DMD (July 2022) JKS2GMU (October 2022) JKS2GNI (October 2022) KBS2EMH (January 2023) KCS11MO (February 2023) KES2KMS (April 2023) KDS1CNG (March 2023) KHS25MQ (July 2023) KJS3SMN (October 2023)

Allowed and prohibited medications

Any concomitant medication deemed necessary for the welfare of the patient during the study was permitted at the discretion of the investigator.

The following concomitant medications were prohibited during the study:

- Any biosimilar of ustekinumab or any drug that directly targets IL-12 or IL-23;
- Any biologic agents approved for the treatment of psoriasis;
- Any conventional systemic therapy that could affect psoriasis (including, but not limited to, methotrexate, cyclosporine);
- Any systemic steroids that could affect psoriasis;
- Topical therapies for the treatment of psoriasis (including, but not limited to, corticosteroids, vitamin D analogues, calcineurin inhibitors, or retinoids);

- Topical corticosteroids for the treatment of indications other than psoriasis were allowed during the study with the limited situations for topical effect (otic, nasal or inhaled) within recommended dose and for 14 consecutive days or less;
- Ultraviolet A phototherapy (with or without oral psoralen) or ultraviolet B phototherapy for the treatment of psoriasis;
- Any investigational drug;
- Initiation or dose modification of drugs that may aggravate psoriasis (e.g., beta-blockers, lithium, antimalarials);
- Herbal treatment that could affect psoriasis;
- Live or live-attenuated vaccination during the study and at least 15 weeks after the last dosing of study drug (Note: inactivated vaccines were acceptable during the study);
- BCG vaccination during the study and 1 year after the last dosing of study drug.

- **Objectives**

Primary Study Objective

The primary objective of the study was to demonstrate that CT-P43 is equivalent to EU-Stelara, in terms of efficacy as determined by the mean percent improvement from baseline in PASI score at Week 12.

Secondary Study Objectives

To evaluate efficacy, PK, QoL, and overall safety including immunogenicity up to Week 52.

Exploratory objective

To evaluate additional efficacy up to Week 52 and to characterise biomarker.

- **Outcomes/endpoints**

Primary efficacy endpoint

1. Percent improvement in Psoriasis Area and Severity Index (PASI) from Baseline to Week 12.

Secondary efficacy endpoints

1. The PASI scores at Weeks 0, 2, 4, 8, 12, 16, 28, 40, and 52;
2. The mean percent improvement from baseline in PASI score at Weeks 2, 4, 8, 16, 28, 40, and 52;
3. The proportion of patients who achieve at least 50/75/90/100% improvement from baseline in PASI (PASI 50/75/90/100) at Weeks 2, 4, 8, 12, 16, 28, 40, and 52;
4. The proportion of patients with static Physician Global Assessment (sPGA) score on a 5-point scale of clear (0) or almost clear (1) at Weeks 0, 2, 4, 8, 12, 16, 28, 40, and 52;
5. The change in Dermatology Life Quality Index (DLQI) score from baseline at Weeks 2, 4, 8, 12, 16, 28, 40, and 52.

PK assessments

1. The serum concentration was to be assessed at Weeks 0, 4, 12, 16, 28, 40, and 52.

Immunogenicity Assessments

1. Proportion of patients with anti-ustekinumab antibody and neutralising anti-body.

Safety assessments

1. Frequency, type, and severity of treatment-emergent adverse events (TEAEs) including adverse drug reactions (ADRs);
2. Frequency and severity of ISRs;
3. Routine safety parameters, including laboratory safety, vital sign measurements, 12-lead electrocardiogram (ECG) results, chest X-ray, and physical examination findings.

- **Sample size**

A total sample size was planned to be a minimum of 446 patients (a minimum of 223 patients in each treatment group of CT-P43 and Stelara). Considering that the drop-out rate had been hypothesised at 10%, a minimum sample size of 400 patients (a minimum of 200 patients in each treatment group of CT-P43 and Stelara) was estimated for the purpose of safety follow-up in enough number of patients. The patients who were administered only 45 mg of study drug (CT-P43 and Stelara) in Treatment Period I were included in the assessment of therapeutic equivalence. A sample size of 166 patients (83 patients in each treatment group of CT- P43 and Stelara) was estimated to provide 80% statistical power for the demonstration of similarity of the mean percent improvement from change baseline in the PASI score at Week 12 with an equivalence margin of -15% to 15% using 95% confidence interval (CI) approach corresponding to two one-sided test with 2.5% significance level. The sample size assumed that the standard deviation (SD) of the percent improvement in PASI score at Week 12 is 29.6 and the expected difference to be 0.

- **Randomisation and Blinding (masking)**

Randomisation

An interactive web response system (IWRS) was used for the randomisation. Randomisation statistician generated the randomisation schedule for IWRS, which linked sequential patient randomisation numbers to treatment codes.

Patients were randomly assigned at Day 1 (Week 0) to receive CT-P43 or EU-Stelara using a 1:1 allocation ratio.

The first randomisation to treatment assignment was stratified by the following:

- Country
- Body weight (≤ 100 kg vs. > 100 kg)
- Prior biologic use approved for psoriasis treatment (Yes or No)

Prior to dosing at Week 16, patients in the EU-Stelara group were randomly assigned again in a ratio of 1:1 to either continue EU-Stelara or undergo transition to CT-P43 from Week 16. All patients who were initially randomly assigned to CT-P43 at Day 1 (Week 0) continued their treatment with CT-P43 until Week 40. The second randomisation was also conducted in the CT- P43 group prior to dosing at Week 16 to maintain the study blind. The second randomisation for the EU-Stelara group was stratified by dose at Week 16 (45 mg vs. 90 mg).

Blinding (masking)

This was a double-blind study. The blind was to be broken only if specific emergency treatment was dictated as knowing the study drug assignment was required for medical management. In such cases,

the investigator could, in an emergency, determine the identity of the study drug by using the applicable procedure in the IWRS.

The date, time, and reason for the unblinding were to be documented in the appropriate field of the eCRF and source documents. The medical monitor was to be informed as soon as possible. Any patients for whom the blind was broken could continue in the study and receive the study drug at the investigator's discretion.

Appropriate physical measures were carried out to maintain blinding of subjects and assessment personnel to the treatment allocation.

- **Statistical methods**

All statistical analyses were conducted using SAS software (SAS Institute Inc., Cary, North Carolina, United States of America [USA]) Version 9.4 or higher.

Continuous data were summarised using descriptive statistics:

- Minimum and maximum were presented to the same number of decimal places as reported.
- Mean, median, geometric mean and percent coefficient of variation (CV%) were rounded to one more decimal place than the maximum decimal place of values in the source listing.
- SD was rounded to one more decimal place than mean.
- Point estimate and confidence intervals (CIs) obtained from statistical procedures were displayed to two decimal places.

Geometric mean was not reported if the dataset included zero values and CV% was not reported if the mean was zero.

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

If there are repeated measurements at a time point, the initial scheduled measurement at that time point was used in the summary tables.

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

Analysis sets

The analysis sets were defined as follows:

- Intent-to-Treat (ITT) Set

The ITT Set consisted of all patients enrolled and randomly assigned to receive a dose of either of the study drug (CT-P43 or Stelara).

- ITT – Treatment Period II Subset

The ITT – Treatment Period II Subset was defined as all patients in ITT Set who were randomly assigned to receive study drug (CT-P43 or Stelara) prior to dosing at Week 16.

- Full Analysis Set (FAS)

The FAS was defined as all patients who were randomly assigned and received at least 1 full dose of study drug (CT-P43 or Stelara).

- Full Analysis Set (FAS) – Treatment Period II Subset

The FAS – Treatment Period II Subset was defined as all patients in FAS who were randomly assigned at Week 16 prior to dosing and received at least 1 full dose of study drug (CT-P43 or Stelara) at or after Week 16.

- Per-Protocol Set (PPS)

The PPS was defined as all randomly assigned patients who received the full dose of study drug (CT-P43 or Stelara) at Weeks 0 and 4 and had a PASI assessment at baseline and Week 12. The patients who had any major protocol deviation which affected the interpretation of study results of primary efficacy endpoint were excluded from PPS. Final determinations of the PPS were made at the blinded DRM held in accordance with ICH harmonised guideline E9.

- Pharmacokinetic (PK) Set

The PK Set consisted of all randomly assigned patients who received at least 1 full dose of either of the study drugs and had at least 1 post-treatment PK concentration data with an above the lower limit of quantification. If any patients were 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 DRM.

- PK – Treatment Period II Subset

The PK – Treatment Period II Subset consisted of all patients in PK Set who received at least 1 full dose of either of the study drugs and had at least 1 post-treatment PK data with an above the lower limit of quantification at or after Week 16.

- Safety Set

The Safety Set was defined as all randomly assigned patients who received at least 1 dose (full or partial) of study drug (CT-P43 or Stelara).

- Safety – Treatment Period II Subset

The Safety – Treatment Period II Subset consisted of all patients in Safety Set who received at least 1 dose (full or partial) of study drug (CT-P43 or Stelara) at or after Week 16.

Primary efficacy analysis

The primary endpoint was the mean percent improvement from baseline in PASI score at Week 12. The primary efficacy analysis and sensitivity analysis on primary efficacy endpoint was conducted on the FAS unless otherwise specified. All analyses for the secondary efficacy endpoints and exploratory efficacy analysis were conducted on for the FAS, PPS, and FAS – Treatment Period II Subset at specified visits unless otherwise specified.

All efficacy listings were based on the ITT Set.

The equivalence test was conducted with patients who were administered at least one 45 mg of study drug and have never received 90 mg of study drug in Treatment Period I. The primary efficacy analysis was conducted on the FAS using an analysis of covariance (ANCOVA) model considering the treatment as a fixed effect and country, baseline body weight, prior biologic use approved for psoriasis treatment and baseline PASI score as covariates. A supportive analysis for the primary efficacy endpoint was conducted on the PPS.

For the demonstration of efficacy, point estimate and 95% CI for the difference in the mean percent improvement in PASI between the CT-P43 and Stelara was produced. Therapeutic equivalence of clinical response based on the mean percent improvement from baseline in PASI score at Week 12 was concluded if the 95% CI for the treatment difference was entirely within –15% to 15%.

Sensitivity analyses

An imputation method for sensitivity analysis was Multiple imputation (MI) with the Missing at random (MAR) assumption using MI procedure in SAS. The multiple imputed datasets were generated based on regression models with country, baseline body weight, prior biologic use approved for psoriasis treatment, baseline PASI score and treatment group as covariates. All patients with baseline PASI score in FAS were included in the analysis. Ten imputed datasets were created and, in the case that the imputed value of percent improvement from baseline in PASI score at Week 12 was over 100, it was replaced with 100. ANCOVA for the mean percent improvement in PASI at Week 12 was applied to each of the imputed datasets. The results from each set of imputed datasets were then be combined using MIANALYZE procedure in SAS based on Rubins' rules for final statistical inference. For the demonstration of efficacy, point estimate and 95% CI for the difference in the mean percent improvement from baseline in PASI score at Week 12 between CT-P43 and Stelara was computed. Therapeutic equivalence of clinical response was concluded if the 95% CI for treatment difference was entirely within -15% to 15%.

To assess the robustness, sensitivity analysis using tipping point analyses under Missing Not at Random (MNAR) scenario was to be performed for the primary efficacy endpoint in the FAS. Since the imputed values were out of range of PASI score, that is, all possible scenarios in tipping point analysis are entirely within the equivalence margin, 'best-worst case' and 'worst-best case' sensitivity analyses were presented. First, a 'best-worst case' scenario dataset was generated on the assumption that the missing values in CT-P43 were imputed with '100' percent meaning that PASI scores at Week 12 go down to all zeros, and the missing values in EU-Stelara were imputed with '0' percent meaning that PASI scores at Week 12 remain unchanged from baseline. Then a 'worst-best case' scenario dataset was generated on the premise that the missing values in CT-P43 were imputed with '0' percent and the missing values in EU-Stelara were imputed with '100' percent. Point estimate and 95% CI for treatment difference was also provided using an ANCOVA considering the treatment as a fixed effect and country, baseline body weight, prior biologic use approved for psoriasis treatment and baseline PASI score as covariates under the scenarios.

Secondary efficacy analysis

All analyses for the secondary efficacy endpoints were conducted on for the FAS, PPS and FAS – Treatment Period II Subset at the time points specified in the schedule of events. The following parameters were analysed as secondary efficacy endpoints:

- The PASI scores at Weeks 0, 2, 4, 8, 12, 16, 28, 40, and 52
- The mean percent improvement from baseline in PASI score at Weeks 2, 4, 8, 16, 28, 40, and 52
- The proportion of patients who achieve at least PASI 50/75/90/100 at Weeks 2, 4, 8, 12, 16, 28, 40, and 52
- The proportion of patients with sPGA score on a 5-point scale of clear (0) or almost clear (1) at Weeks 0, 2, 4, 8, 12, 16, 28, 40, and 52
- The change in DLQI score from baseline at Weeks 2, 4, 8, 12, 16, 28, 40, and 52

Pharmacokinetic analysis

Descriptive statistics (n, mean, SD, geometric mean, CV%, minimum, median, and maximum) for serum concentrations were presented by treatment group and dose of study drug. The dose of study drug prior to Week 16 was classified depending on the dose at Week 0, and the dose on or after Week 16 was classified depending on the dose at Week 16.

Immunogenicity analysis

The results of immunogenicity were summarised for Overall Period on the Safety Set. The number and percentage of patients were presented by treatment group and test at each scheduled visit.

The positive conversion in ADA and NAb were also be summarised including all scheduled and unscheduled visits.

The proportion of patients who reported at least one ADA positive result between each first study drug administration of Treatment Period I and Treatment Period II in patients who had at least one ADA result between each first study drug administration of Treatment Period I and Treatment Period II and had not any ADA positive result before the first study drug administration was presented for the Safety Set.

The proportion of patients who reported at least one NAb positive result between each first study drug administration of Treatment Period I and Treatment Period II in patients who had at least one ADA result between each first study drug administration of Treatment Period I and Treatment Period II and had not any NAb positive result before the first study drug administration were presented for the Safety Set.

For the Safety – Treatment Period II Subset, proportion of patients who reported at least one ADA positive result after the first study drug administration in Treatment Period II in patients who had at least one ADA result after the first study drug administration in Treatment Period II and had not any ADA positive result before the first study drug administration in Treatment Period II were presented.

The proportion of patients who reported at least one NAb positive result after the first study drug administration in Treatment Period II in patients who had at least one ADA result after the first study drug administration in Treatment Period II and had not any NAb positive result before the first study drug administration in Treatment Period II were also be presented.

Results

- **Participant flow**

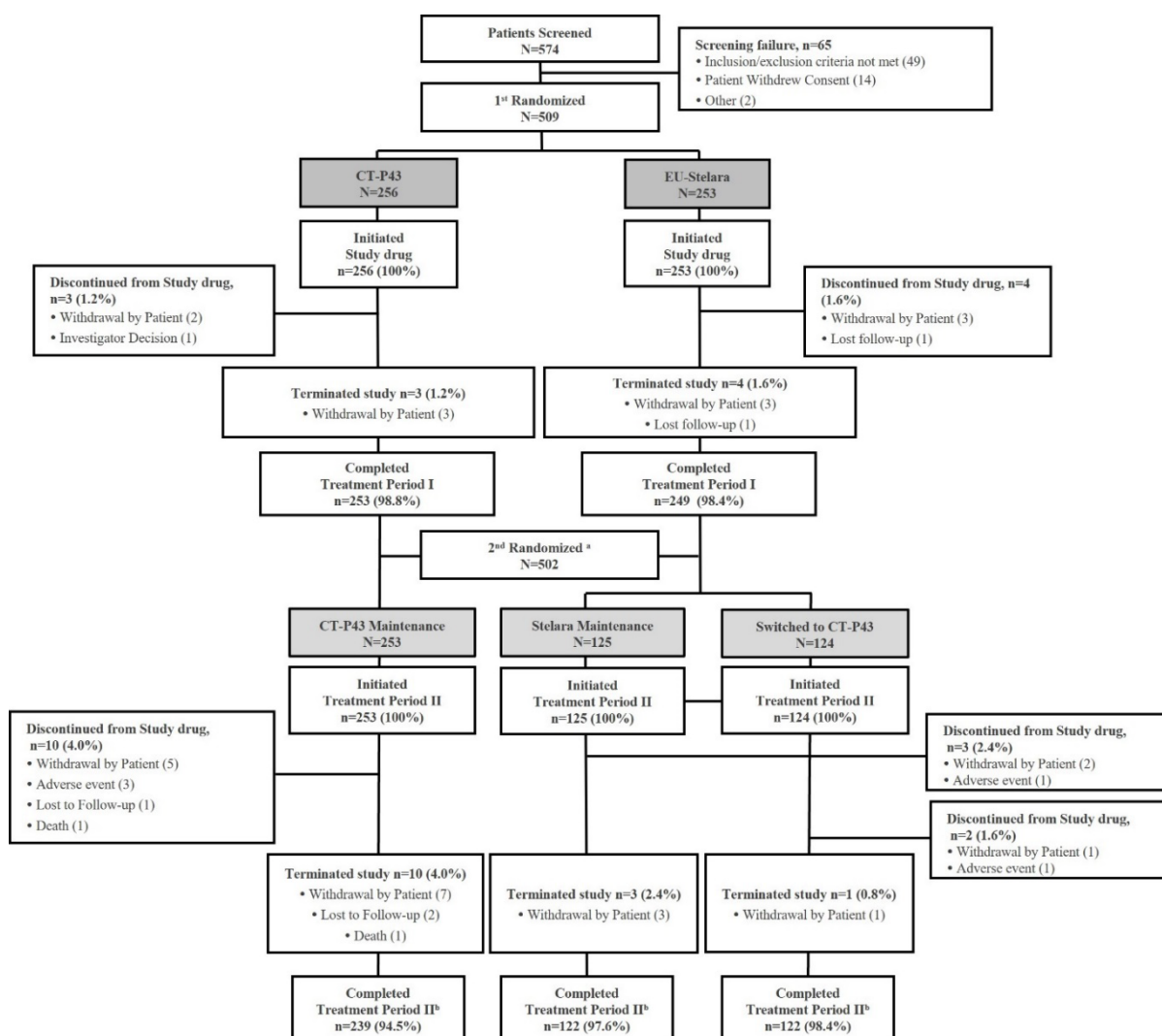


Figure 4. Summary of Patient Disposition (Treatment Period I and II): ITT Set and ITT – Treatment Period II Subset

• Recruitment

A total of 574 patients were screened and 509 patients from 34 study centres in 4 countries were enrolled in this study. 256 patients were initially randomly assigned to CT-P43 group, and 253 patients were initially randomly assigned to EU-Stelara group.

First patient had their first visit on 11 January 2021. Last patient had their last visit on 12 May 2022.

- **Conduct of the study**

Protocol amendments

The original protocol, (Version 1.0), dated 03 July 2020 was amended 5 times during the study period.

- Global protocol amendment, dated 10 August 2020 (Version 1.1)
- Korea-specific protocol amendment, dated 18 December 2020 (Version 1.1_A.0)
- Global protocol amendment, dated 05 July 2021 (Version 2.0)
- US-specific protocol amendment (B.0), dated 14 July 2021 (Version 2.0_B.0)
- Korea-specific protocol amendment (A.0), dated 22 July 2021 (Version 2.0_A.0)

Protocol deviations

Treatment Period 1

Table 25. Major protocol deviations and other reasons for exclusion from the analysis set (treatment period I): all randomly assigned patients

	CT-P43 (N=256)	Stelara (N=253)	Total (N=509)	Excluded Sets ¹
	Number (%) of patients			
Major protocol deviation				
Receipt of prohibited medication or treatment which affect Week 12 efficacy assessment	3 (1.2%)	3 (1.2%) ²	6 (1.2%)	PPS
Other reasons for exclusion				
Dose not complete at Weeks 0 and 4	1 (0.4%)	4 (1.6%) ^{2, 3}	5 (1.0%)	PPS
No efficacy data at baseline or Week 12	0	5 (2.0%) ³	5 (1.0%)	PPS
No post-treatment PK concentration data	0	5 (2.0%)	5 (1.0%)	PK

Abbreviations: PPS, Per-protocol Set; PK, Pharmacokinetic Set.

Note: The actual number of patients is summarized for each corresponding category.

1. Protocol deviation excluded patients from the following sets.
2. A patient (Patient ████████) in the EU-Stelara group was excluded from PPS due to the major protocol deviation and not meeting of the definition of PPS (Receipt of prohibited medication or treatment which affect Week 12 efficacy assessment and Dose not complete at Weeks 0 and 4).
3. Two patients (Patient ████████, ████████) in the EU-Stelara group were excluded from PPS due to not meeting of the definition of PPS (Dose not complete at Week 0 and 4, No efficacy data at baseline or Week 12).

Treatment Period 2

No major protocol deviations were reported during Treatment Period II.

Table 26. Major protocol deviations and other reasons for exclusion from the analysis subset (treatment period II): ITT – treatment period II subset

	CT-P43 Maintenance (N=253)	Stelara Maintenance (N=125)	Switched to CT-P43 (N=124)	Total (N=502)	Excluded Subset
	Number (%) of patients				
Major protocol deviation	0	0	0	0	-
Other reasons for exclusion					
No post-treatment PK concentration data	0	0	2 (1.6%)	2 (0.4%)	PK2
No PK concentration data in Treatment Period II	5 (2.0%)	7 (5.6%)	5 (4.0%)	17 (3.4%)	PK2

Abbreviations: ITT, intent-to-treat; PK, pharmacokinetic; PK2, Pharmacokinetic – Treatment Period II.

COVID-19 Related Protocol Deviations

Due to COVID-19 pandemic, a total of 8 (1.6%) patients missed study visits (4 [1.6%] patients in the CT-P43 group and 4 [1.6%] patients in the EU-Stelara group) up to Week 12. Among these patients, a total of 3 patients (one patient in the CT-P43 group and two patients in the EU-Stelara group) were excluded from PPS due to the major protocol deviation or not meeting of the definition of PPS.

The COVID-19 pandemic did not result in any of the patients missing the study visit at Week 12, the time point for the primary endpoint assessment.

- **Baseline data**

Table 27. Demographics and stratification details: ITT set

	CT-P43 (N=256)	Stelara (N=253)	Total (N=509)
Age (years)			
n	256	253	509
Mean (SD)	42.6 (13.00)	42.2 (12.64)	42.4 (12.81)
Median	41.0	41.0	41.0
Min, Max	18, 74	18, 77	18, 77
Gender, n (%)			
Male	161 (62.9%)	173 (68.4%)	334 (65.6%)
Female	95 (37.1%)	80 (31.6%)	175 (34.4%)
Female fertility status¹, n (%)			
Post-menopausal	36 (37.9%)	26 (32.5%)	62 (35.4%)
Potentially able to bear children	59 (62.1%)	54 (67.5%)	113 (64.6%)
Race, n (%)			
Asian	25 (9.8%)	23 (9.1%)	48 (9.4%)
White	231 (90.2%)	230 (90.9%)	461 (90.6%)
Ethnicity, n (%)			
Hispanic or Latino	1 (0.4%)	1 (0.4%)	2 (0.4%)
Non-Hispanic or Non-Latino	255 (99.6%)	252 (99.6%)	507 (99.6%)
Height (cm) at Screening			
n	256	253	509
Mean (SD)	173.11 (9.956)	172.94 (9.602)	173.03 (9.772)
Median	173.95	174.00	174.00
Min, Max	151.7, 213.0	141.0, 195.0	141.0, 213.0
Weight (kg) at baseline			
n	256	253	509
Mean (SD)	85.09 (19.775)	85.65 (18.998)	85.36 (19.375)
Median	84.25	86.00	85.50
Min, Max	41.0, 168.0	46.1, 151.5	41.0, 168.0
Body mass index (kg/m²) at baseline			
n	256	253	509
Mean (SD)	28.229 (5.3788)	28.588 (5.8182)	28.407 (5.5989)
Median	27.515	27.920	27.770
Min, Max	15.82, 46.54	15.85, 48.36	15.82, 48.36
Country, n (%)			
Estonia	5 (2.0%)	6 (2.4%)	11 (2.2%)
Korea	25 (9.8%)	23 (9.1%)	48 (9.4%)

	CT-P43 (N=256)	Stelara (N=253)	Total (N=509)
Poland	189 (73.8%)	188 (74.3%)	377 (74.1%)
Ukraine	37 (14.5%)	36 (14.2%)	73 (14.3%)
Baseline body weight category, n (%)			
≤100 kg	198 (77.3%)	199 (78.7%)	397 (78.0%)
>100 kg	58 (22.7%)	54 (21.3%)	112 (22.0%)
Prior biologic use approved for psoriasis treatment, n (%)			
Yes	38 (14.8%)	44 (17.4%)	82 (16.1%)
No	218 (85.2%)	209 (82.6%)	427 (83.9%)

Abbreviations: ITT, intent-to-treat; Max, maximum; Min, minimum; SD, standard deviation.

¹ Percentages were calculated by using the number of female patients as the denominator.

- **Numbers analysed**

All enrolled patients in the CT-P43 and EU-Stelara groups were included in the ITT Set. The number of patients in each of the analysis sets was generally similar between the CT-P43 and EU-Stelara groups.

A total of 502 patients were included in the ITT – Treatment Period II Subset (253 patients, 125 patients, and 124 patients in the CT-P43 maintenance, EU-Stelara maintenance and switched to CT-P43 groups, respectively). The proportion of patients in each of the other analysis subsets was generally similar as distributed in ITT – Treatment Period II Subset.

Table 1 Analysis sets (treatment period I)

Analysis set	CT-P43	Stelara	Total
	Number of patients		
Intent-to-Treat (ITT) set	256	253	509
Full Analysis Set (FAS)	256	253	509
Per-protocol set (PPS)	252	244	496
Pharmacokinetic (PK) set	256	248	504
Safety set	256	253	509

Abbreviations: FAS, Full Analysis Set; ITT, intent-to-treat; PK, pharmacokinetic; PPS, Per-protocol Set.

Note: The numbers of patients in the ITT Set, FAS, and PPS were presented by the treatment group assigned from first randomization. For the Safety Set and PK Set, patients were counted in treatment group based on the study drug they actually received.

Table 28. Analysis sets (treatment period II)

Subset	CT-P43 Maintenance	Stelara Maintenance	Switched to CT-P43	Total
	Number of patients			
ITT – Treatment Period II Subset	253	125	124	502
FAS – Treatment Period II Subset	253	125	124	502
PK – Treatment Period II Subset	248	118	117	483
Safety – Treatment Period II Subset	253	125	124	502

Abbreviations: FAS, Full Analysis Set; ITT, intent-to-treat; PK, pharmacokinetic.

Note: The numbers of patients in the ITT – Treatment Period II Subset and FAS – Treatment Period II Subset are presented by the treatment group assigned from the second randomization. For the Safety – Treatment Period II Subset and PK – Treatment Period II Subset, patients were counted in treatment group based on the study drug they actually received.

- **Outcomes and estimation**

Primary endpoint

The primary efficacy endpoint was the mean percent improvement from baseline in PASI score at Week 12. The equivalence test was conducted with patients who were administered at least one 45 mg of study drug and had never received 90 mg of study drug in Treatment Period I. The primary efficacy analysis was conducted on the FAS using an ANCOVA model. For the demonstration of efficacy, the point estimate and 95% CI for the estimate of treatment difference was entirely within the predefined equivalence margin of –15% to 15%, which demonstrated therapeutic equivalence between the CT-P43 and EU-Stelara groups in the mean percent PASI score improvement from baseline at Week 12 (95% CI: [-2.29, 4.16] for the FAS and [-2.32, 4.07] for the PPS).

Table 29. Mean Percent Improvement from Baseline in PASI Score at Week 12 (ANCOVA) in Study CT-P43 3.1 (FAS and PPS)

Treatment Group	n	LS Mean (SE)	Estimate of Treatment Difference (%)	95% CI of Treatment Difference (%)
FAS				
CT-P43	198	78.26 (2.054)	0.94	(-2.29, 4.16)
EU-Stelara	194	77.33 (2.049)		
PPS				
CT-P43	195	78.41 (2.038)	0.87	(-2.32, 4.07)
EU-Stelara	193	77.54 (2.025)		

Note: An ANCOVA was performed with the treatment as a fixed effect and country, baseline body weight, prior biologic use approved for psoriasis treatment and baseline PASI score as covariates. Adjusted LS means and SE, estimate of treatment difference [CT-P43 – EU-Stelara] and 95% CI calculated from the ANCOVA model.

Abbreviation: LS, least squares; n, the number of patients administered each treatment; SE, standard error

Subgroup analysis by ADA status at Week 12

The mean percent improvement from baseline in the PASI score at Week 12 for the ADA positive and ADA negative subgroups of the FAS was similar regardless of ADA positivity and was also comparable between the 2 groups in both ADA positive and negative subgroups.

Table 30. Percent improvement from baseline in PASI score at week 12 by ADA status at week 12: FAS

Week 12 ADA positive subgroup¹	CT-P43 (N=16)	Stelara (N=41)
Statistic		
n	16	41
Mean	82.72	80.59
SD	22.850	22.602
Minimum	5.4	0.0
Median	89.32	89.09
Maximum	100.0	100.0
Week 12 ADA negative subgroup¹	CT-P43 (N=182)	Stelara (N=153)
Statistic		
n	182	153
Mean	85.60	85.32
SD	14.742	16.368
Minimum	38.4	24.4
Median	89.33	91.84
Maximum	100.0	100.0

Abbreviations: ADA, anti-drug antibody; FAS, Full Analysis Set; PASI, Psoriasis Area and Severity Index; SD, standard deviation.

Note: If any individual component was missing, the PASI score was not calculated. The patients who administered at least one 45 mg for study drug and never received 90 mg of study drug in Treatment Period I were subject to analysis.

¹ In the FAS, patients who showed a “Positive” result in an immunogenicity test obtained at Week 12 were considered as “ADA positive subgroup.” All patients who have a “Negative” result in a post-treatment immunogenicity test at Week 12 were considered as “ADA negative subgroup.”

Sensitivity analysis: Percent Improvement from Baseline to Week 12 in PASI

As a sensitivity analysis, an ANCOVA for the mean percent improvement from baseline in PASI at Week 12 with missing data imputation was conducted. Multiple imputation (MI) with the MAR assumption was used for the imputation method. The estimated 95% CI between CT-P43 and EU-Stelara group was entirely within the predefined equivalence margin of -15% to 15% (95% CI: [-2.23, 4.16] for the FAS).

Table 31. Mean percent improvement from baseline in PASI score at week 12 (ANCOVA) – Multiple imputation (MI): FAS

Treatment Group	n	LS Mean (SE)	Estimate of Treatment Difference	95% CI of Treatment Difference (%)
FAS				
CT-P43	198	78.25 (2.053)	0.96	(-2.23, 4.16)
Stelara	199	77.29 (2.041)		

Abbreviations: CI, confidence interval; FAS, Full Analysis Set; LS, least squares; SE, standard error.

Note: An ANCOVA was performed with the treatment as a fixed effect and country, baseline body weight, prior biologic use approved for psoriasis treatment and baseline PASI score as covariates. Imputation with the missing at random (MAR) assumption was used for missing data imputation. For the case that the imputed value of percent improvement from baseline in PASI score at Week 12 is over 100, it was replaced with 100. Final statistical inference based on Rubin’s rule was displayed by combining the results from each set of imputed datasets. Adjusted least squares means and standard error, estimate of treatment difference [CT-P43 – Stelara] and 95% confidence interval calculated from the ANCOVA model. The patients who administered at least one 45 mg for study drug and never received 90 mg of study drug in Treatment Period I were subject to analysis.

Secondary endpoints

- Psoriasis Area and Severity Index at Weeks 0, 2, 4, 8, 12 and 16

The PASI scores for the FAS (Treatment Period I) and FAS – Treatment Period II Subset (Treatment Period II and up to EOS) are summarised below.

Treatment Period 1

The PASI scores during Treatment Period I were similar between the CT-P43 and EU-Stelara groups in the FAS and PPS.

Table 32. The PASI score: FAS

Visit Statistic	CT-P43 (N=256)	Stelara (N=253)	Estimate of Treatment Difference (%)	95% CI of Treatment Difference (%)
Baseline				
n	256	253		
Mean	21.51	20.88	0.63	(-0.76, 2.02)
SD	7.939	7.998		
Minimum	12.0	12.0		
Median	19.65	18.80		
Maximum	50.3	56.7		
Week 2				
n	252	251		
Mean	17.48	17.21	0.27	(-1.06, 1.61)
SD	7.625	7.637		
Minimum	0.5	1.5		
Median	16.60	16.20		
Maximum	47.4	55.2		
Week 4				
n	254	249		
Mean	12.91	13.08	-0.17	(-1.34, 1.00)
SD	6.476	6.884		
Minimum	0.0	0.0		
Median	12.05	12.30		
Maximum	37.7	47.2		

Visit Statistic	CT-P43 (N=256)	Stelara (N=253)	Estimate of Treatment Difference (%)	95% CI of Treatment Difference (%)
Week 8				
n	255	250		
Mean	6.14	6.49	-0.35	(-1.25, 0.55)
SD	4.794	5.493		
Minimum	0.0	0.0		
Median	5.40	5.40		
Maximum	27.8	33.5		
Week 12				
n	256	248		
Mean	2.98	3.44	-0.46	(-1.14, 0.23)
SD	3.412	4.362		
Minimum	0.0	0.0		
Median	1.95	1.80		
Maximum	26.1	22.8		
Week 16				
n	254	248		
Mean	2.02	2.61	-0.58	(-1.19, 0.03)
SD	2.942	3.943		
Minimum	0.0	0.0		
Median	0.90	1.20		
Maximum	26.0	24.8		

Abbreviations: CI, confidence interval; FAS, Full Analysis Set; PASI, Psoriasis Area and Severity Index; SD, standard deviation.

Note: If any individual component was missing, the PASI score was not calculated. The difference on the mean and its 95% CI of the 2 treatment groups was produced using a t-test.

Treatment Period 2 and Follow Up to EOS

Although the PASI score at Week 16 was slightly higher in the Switched to CT-P43 group, the PASI scores were generally similar among the CT-P43 maintenance, EU-Stelara maintenance and Switched to CT-P43 groups in the FAS – Treatment Period II Subset during Treatment Period II and up to EOS.

Table 33. The PASI score: FAS – treatment period II subset

Visit Statistic	CT-P43 Maintenance (N=253)	Stelara Maintenance (N=125)	Switched to CT-P43 (N=124)
Week 16			
n	253	124	124
Mean	2.03	2.40	2.81
SD	2.946	3.500	4.346
Minimum	0.0	0.0	0.0
Median	0.90	1.20	1.20
Maximum	26.0	21.4	24.8
Week 28			
n	251	124	124
Mean	1.12	1.51	1.68
SD	2.124	2.776	2.719
Minimum	0.0	0.0	0.0
Median	0.30	0.60	0.60
Maximum	20.0	15.0	15.9
Week 40			
n	246	124	123
Mean	1.09	1.51	1.38
SD	2.005	2.850	1.964
Minimum	0.0	0.0	0.0
Median	0.00	0.40	0.60
Maximum	14.3	15.8	9.2
EOS			
n	242	122	123
Mean	1.44	1.33	1.93
SD	2.921	3.070	2.966
Minimum	0.0	0.0	0.0
Median	0.10	0.15	0.60
Maximum	17.6	18.4	14.9

Abbreviations: EOS, end-of-study; FAS, Full Analysis Set; PASI, Psoriasis Area and Severity Index; SD, standard deviation.

Note: If any individual component was missing, the PASI score was not calculated.

- Percent Improvement in Psoriasis Area and Severity Index from Baseline

Treatments Period 1

The mean percent improvement from baseline in PASI score was generally similar between the CT-P43 and EU-Stelara groups in the FAS and PPS during Treatment Period I.

Table 34. Percent improvement from baseline in PASI score: FAS

Visit Statistic	CT-P43 (N=256)	Stelara (N=253)	Estimate of Treatment Difference (%)	95% CI of Treatment Difference (%)
Week 2				
n	252	251		
Mean	19.02	17.34	1.68	(-1.63, 4.98)
SD	19.591	18.124		
Minimum	-45.3	-27.5		
Median	13.98	14.21		
Maximum	96.4	89.6		
Week 4				
n	254	249		
Mean	39.46	37.29	2.17	(-1.78, 6.12)
SD	22.225	22.853		
Minimum	-47.3	-25.3		
Median	38.40	33.78		
Maximum	100.0	100.0		
Week 8				
n	255	250		
Mean	70.96	68.55	2.41	(-1.39, 6.21)
SD	20.584	22.876		
Minimum	13.0	-16.7		
Median	74.24	73.51		
Week 12				
n	256	248		
Mean	86.05	83.99	2.07	(-0.77, 4.90)
SD	14.833	17.484		
Minimum	5.4	0.0		
Median	90.21	90.69		
Maximum	100.0	100.0		
Week 16				
n	254	248		
Mean	90.68	88.10	2.58	(0.06, 5.11)
SD	12.477	16.127		
Minimum	5.8	-16.7		
Median	95.59	93.61		
Maximum	100.0	100.0		

Abbreviations: CI, confidence interval; FAS, Full Analysis Set; PASI, Psoriasis Area and Severity Index; SD, standard deviation.

Note: If any individual component was missing, the PASI score was not calculated. The difference on the mean and its 95% CI of 2 treatment groups was produced using a t-test.

Treatment Period 2 and Follow up to EOS

The mean percent improvement from baseline in PASI score was similar among the CT-P43 maintenance, EU-Stelara maintenance and switched to CT-P43 groups in the FAS – Treatment Period II Subset during Treatment Period II and up to EOS.

Table 35. Percent improvement from baseline in PASI score: FAS – treatment period II subset

Visit Statistic	CT-P43 Maintenance (N=253)	Stelara Maintenance (N=125)	Switched to CT-P43 (N=124)
Week 16			
n	253	124	124
Mean	90.64	88.01	88.18
SD	12.488	16.456	15.858
Minimum	5.8	-16.7	0.0
Median	95.59	93.61	93.58
Maximum	100.0	100.0	100.0
Week 28			
n	251	124	124
Mean	95.07	92.55	92.86
SD	8.303	13.704	10.609
Minimum	27.5	-5.0	42.2
Median	98.77	97.62	97.20
Maximum	100.0	100.0	100.0
Week 40			
n	246	124	123
Mean	95.31	92.44	94.00
SD	7.734	14.917	8.439
Minimum	54.2	-1.7	53.3
Median	100.00	97.79	96.61
Maximum	100.0	100.0	100.0
EOS			
n	242	122	123
Mean	93.79	93.39	91.58
SD	11.794	14.947	13.264
Minimum	39.0	8.5	25.6
Median	99.73	99.28	96.48
Maximum	100.0	100.0	100.0

Abbreviations: EOS, end-of-study; FAS, Full Analysis Set; PASI, Psoriasis Area and Severity Index; SD, standard deviation.

Note: If any individual component was missing, the PASI score was not calculated.

The EOS visit was performed at the Week 52 visit for the patients who completed or discontinued study drug.

- Psoriasis Area and Severity Index 50, 75, 90, and 100 Response Rates

Treatment Period 1

The proportions of patients achieving PASI 50, PASI 75, PASI 90, and PASI 100 responses during Treatment Period I were similar between the CT-P43 and EU-Stelara groups in the FAS and PPS.

At Week 12, 96.5%, 82.8%, 50.4%, and 18.4% of the CT-P43 group and 94.9%, 73.9%, 50.2%, and 19.0% of the EU-Stelara group had PASI 50, PASI 75, PASI 90, and PASI 100 responses, respectively.

Although there was a slight difference in the proportion of PASI 75 responders at Week 12 (estimated treatment difference of 8.90% [95% CI: 1.78, 16.02]), the difference was not observed between the groups in PASI 50, PASI 90, and PASI 100 at Week 12 and in PASI 75 at the other timepoints during Treatment Period I.

Table 36. Proportion of PASI 50/75/90/100 responders: FAS

Parameter Visit	CT-P43 (N=256)	Stelara (N=253)	Estimate of Treatment Difference (%)	95% CI of Treatment Difference (%)
	Number (%) of Patients			
PASI 50				
Week 2	16 (6.3%)	13 (5.1%)	1.11	(-2.91, 5.14)
Week 4	78 (30.5%)	68 (26.9%)	3.59	(-4.26, 11.44)
Week 8	213 (83.2%)	195 (77.1%)	6.13	(-0.79, 13.04)
Week 12	247 (96.5%)	240 (94.9%)	1.62	(-1.91, 5.16)
Week 16	251 (98.0%)	240 (94.9%)	3.19	(-0.02, 6.39)
PASI 75				
Week 2	7 (2.7%)	4 (1.6%)	1.15	(-1.37, 3.67)
Week 4	17 (6.6%)	20 (7.9%)	-1.26	(-5.78, 3.25)
Week 8	122 (47.7%)	117 (46.2%)	1.41	(-7.26, 10.08)
Week 12	212 (82.8%)	187 (73.9%)	8.90	(1.78, 16.02)
Week 16	226 (88.3%)	209 (82.6%)	5.67	(-0.44, 11.78)
PASI 90				
Week 2	2 (0.8%)	0	0.78	(-0.30, 1.86)
Week 4	4 (1.6%)	8 (3.2%)	-1.60	(-4.24, 1.04)
Week 8	50 (19.5%)	43 (17.0%)	2.54	(-4.17, 9.24)
Week 12	129 (50.4%)	127 (50.2%)	0.19	(-8.49, 8.88)
Week 16	171 (66.8%)	154 (60.9%)	5.93	(-2.41, 14.26)
PASI 100				
Week 2	0	0	0.00	NC
Week 4	2 (0.8%)	1 (0.4%)	0.39	(-0.94, 1.71)
Week 8	12 (4.7%)	15 (5.9%)	-1.24	(-5.14, 2.65)
Week 12	47 (18.4%)	48 (19.0%)	-0.61	(-7.38, 6.16)
Week 16	76 (29.7%)	61 (24.1%)	5.58	(-2.11, 13.26)

Abbreviations: CI, confidence interval; FAS, Full Analysis Set; NC, not calculated; PASI, Psoriasis Area and Severity Index.

Note: Percentages were calculated by using the number of patients in the set as the denominator. The difference on the proportion and its 95% CI of the 2 treatment groups was produced using the Wald method.

Treatment Period II and Follow-up Period (up to EOS)

The proportions of patients achieving PASI 50, PASI 75, PASI 90, and PASI 100 responses during Treatment Period II were similar among the CT-P43 maintenance, EU-Stelara maintenance and switched to CT-P43 groups in the FAS – Treatment Period II Subset.

At EOS visit, 93.3%, 89.3%, 79.4%, and 47.4% of the CT-P43 maintenance group; 94.4%, 92.8%, 81.6%, and 47.2% of the EU-Stelara maintenance group; and 96.0%, 89.5%, 76.6%, and 34.7% of the Switched to CT-P43 group had PASI 50, PASI 75, PASI 90, and PASI 100 responses, respectively.

Although the proportion of PASI 100 responders was slightly lower in the Switched to CT-P43 group at EOS visit, the differences were not observed in the results of the proportion of PASI 50, PASI 75, and PASI 90 responders up to EOS. It should be noted that PASI score at Week 16 (prior to the study drug administration for Treatment Period II) was slightly higher in the Switched to CT-P43 group but the mean percent improvement from baseline in PASI score was similar up to EOS among the CT-P43 maintenance, EU-Stelara maintenance and Switched to CT-P43 groups. In addition, it is also noted that the proportion of patients who exceeded PASI 90 but did not achieve PASI 100 response (PASI > 90 to <100) was higher in the Switched to CT-P43 group than other groups at EOS visit (32.0% [81/253] in the CT-P43 maintenance group, 33.6% [42/125] in the EU-Stelara maintenance group, and 41.9% [52/124] in the Switched to CT-P43 group).

Table 37. Proportion of PASI 50/70/90/100 responders: FAS – treatment period II subset

Parameter Visit	CT-P43 Maintenance (N=253)	Stelara Maintenance (N=125)	Switched to CT-P43 (N=124)
	Number (%) of Patients		
PASI 50			
Week 16	250 (98.8%)	120 (96.0%)	120 (96.8%)
Week 28	250 (98.8%)	121 (96.8%)	123 (99.2%)
Week 40	246 (97.2%)	120 (96.0%)	123 (99.2%)
EOS	236 (93.3%)	118 (94.4%)	119 (96.0%)
PASI 75			
Week 16	225 (88.9%)	104 (83.2%)	105 (84.7%)
Week 28	244 (96.4%)	116 (92.8%)	116 (93.5%)
Week 40	238 (94.1%)	116 (92.8%)	119 (96.0%)
EOS	226 (89.3%)	116 (92.8%)	111 (89.5%)
PASI 90			
Week 16	170 (67.2%)	80 (64.0%)	74 (59.7%)
Week 28	205 (81.0%)	98 (78.4%)	98 (79.0%)
Week 40	202 (79.8%)	95 (76.0%)	102 (82.3%)
EOS	201 (79.4%)	102 (81.6%)	95 (76.6%)
PASI 100			
Week 16	75 (29.6%)	28 (22.4%)	33 (26.6%)
Week 28	116 (45.8%)	46 (36.8%)	45 (36.3%)
Week 40	125 (49.4%)	53 (42.4%)	46 (37.1%)
EOS	120 (47.4%)	59 (47.2%)	43 (34.7%)

Abbreviations: EOS, end-of-study; FAS, Full Analysis Set; PASI, Psoriasis Area and Severity Index.

Note: Percentages were calculated by using the number of patients in the set as the denominator.

- Static Physician's Global Assessment

Treatment Period 1

The proportion of the patients reaching an sPGA score of clear (0) or almost clear (1) was similar during Treatment Period I between the CT-P43 and EU-Stelara groups in the FAS and PPS. The number and proportion of the patients with an sPGA score of clear (0) or almost clear (1) at Week 12 in the FAS was 219 (85.5%) patients in the CT-P43 group and 201 (79.4%) patients in the EU-Stelara group (estimated treatment difference of 6.10% [95% CI: -0.48, 12.68]).

Treatment Period II and Follow-up Period (up to EOS)

The proportion of the patients reaching an sPGA score of clear (0) or almost clear (1) was generally similar during Treatment Period II among the CT-P43 maintenance, EU-Stelara maintenance, and Switched to CT-P43 groups in the FAS – Treatment Period II Subset; except the case that it was lower in the Switched to CT-P43 group compared to CT-P43 and EU-Stelara maintenance groups at EOS visit. The number and proportion of the patients with an sPGA score of clear (0) or almost clear (1) at EOS visit in the FAS – Treatment Period II Subset was 215 (85.0%) patients in the CT-P43 maintenance group, 110 (88.0%) patients in the EU-Stelara maintenance group, and 96 (77.4%) patients in the Switched to CT-P43 group.

- Dermatology Life Quality Index Scores

Treatment Period 1

The mean change from baseline in the DLQI score during Treatment Period I was similar between the CT-P43 group and EU-Stelara group in the FAS and PPS.

The mean (SD) actual DLQI score at baseline in the FAS was 13.2 (7.08) in the CT-P43 group and 11.9 (6.68) in the EU-Stelara group.

A similar reduction (improvement) in the DLQI score from baseline in the FAS was observed at Week 12 between the CT-P43 group and EU-Stelara group (Week 12: mean [SD] change from baseline - 9.7 [6.74] and -8.5 [6.67], respectively; estimated treatment difference -1.15 [95% CI: -2.33, 0.02]).

Treatment Period II and Follow-up Period (up to EOS)

The mean change from baseline in the DLQI score during Treatment Period II and up to EOS was similar among the CT-P43 maintenance, EU-Stelara maintenance and Switched to CT-P43 groups in the FAS – Treatment Period II Subset and the change from baseline was consistent with slight decrease compared to baseline (improvement) up to EOS.

The mean (SD) actual DLQI score at baseline in the FAS – Treatment Period II Subset was 13.2 (7.11) in the CT-P43 maintenance group, 11.6 (6.52) in the EU-Stelara maintenance group, and 12.1 (6.76) in the Switched to CT-P43 group.

A similar reduction (improvement) in DLQI score from baseline was observed at EOS visit among the CT-P43 maintenance, EU-Stelara maintenance and Switched to CT-P43 groups (mean [SD] change from baseline -10.5 [7.24], -8.5 [7.17], and -9.2 [6.93], respectively, in the FAS – Treatment Period II Subset).

The least squares (LS) mean for percent improvement in PASI from baseline to Week 12 was comparable between CT-P43 group (78.26%) and the EU-Stelara group (77.33%). The LS mean difference (CT-P43 vs EU-Stelara) was 0.94% with 95% confidence interval from -2.29% to 4.16%. This is within the pre-specified acceptance range [-15%, 15%] and as the 95% CI was within a narrow range, clinical comparability can be concluded.

Subgroup Analysis by ADA Status at Week 12

The mean percent improvement from baseline in the PASI score at Week 12 for the ADA positive and ADA negative subgroups of the FAS was similar regardless of ADA positivity and was also comparable between the 2 groups in both ADA positive and negative subgroups.

Table 38. Percent improvement from baseline in PASI score at week 12 by ADA status at week 12: FAS

Week 12 ADA positive subgroup ¹	CT-P43 (N=16)	Stelara (N=41)
Statistic		
n	16	41
Mean	82.72	80.59
SD	22.850	22.602
Minimum	5.4	0.0
Median	89.32	89.09
Maximum	100.0	100.0
Week 12 ADA negative subgroup ¹	CT-P43 (N=182)	Stelara (N=153)
Statistic		
n	182	153
Mean	85.60	85.32
SD	14.742	16.368
Minimum	38.4	24.4
Median	89.33	91.84
Maximum	100.0	100.0

Abbreviations: ADA, anti-drug antibody; FAS, Full Analysis Set; PASI, Psoriasis Area and Severity Index; SD, standard deviation.

Note: If any individual component was missing, the PASI score was not calculated. The patients who administered at least one 45 mg for study drug and never received 90 mg of study drug in Treatment Period I were subject to analysis.

¹ In the FAS, patients who showed a “Positive” result in an immunogenicity test obtained at Week 12 were considered as “ADA positive subgroup.” All patients who have a “Negative” result in a post-treatment immunogenicity test at Week 12 were considered as “ADA negative subgroup.”

• Summary of main efficacy results

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

Table 39. Summary of efficacy for trial CT-P43 3.1

Title: A Randomised, Active-Controlled, Double-Blind, Phase 3 Study to Compare the Efficacy and Safety of CT-P43 to Stelara in Patients with Moderate to Severe Plaque Psoriasis			
Study identifier	Project code: CT-P43 EudraCT number: 2020-001045-39		
Design	Randomised, parallel-group, double-blind, multicentre study		
	Duration of Main phase:	Screening Period: Day -42 [up to 6 weeks] to Day -1 Treatment Period: Week 0 to Week 40 - Treatment Period I (16 weeks) - Treatment Period II (24 weeks) Off-dose follow-up period (12 weeks) prior to the EOS visit.	
	Duration of Run-in phase:	Not applicable	
	Duration of Extension phase:	Not applicable	
Hypothesis	To demonstrate that CT-P43 is equivalent to EU-Stelara		
Treatments groups	CT-P43	Patients received CT-P43 45 mg (who weighed ≤100 kg) or 90 mg (who weighed >100 kg) administered subcutaneously at Weeks 0, 4, 16, 28, and 40 based on patient's baseline body weight. Number of randomised = 256	
	EU-Stelara	Patients received EU-Stelara 45 mg (who weighed ≤100 kg) or 90 mg (who weighed >100 kg) administered subcutaneously at Weeks 0, 4, 16, 28, and 40 based on patient's baseline body weight. Number of randomised = 253	
Endpoints and definitions	Primary efficacy endpoint	Mean percent improvement from baseline in PASI score at Week 12	The mean percent improvement from baseline in PASI score at Week 12
	Secondary efficacy endpoints	PASI scores	The PASI scores at Weeks 0, 2, 4, 8, 12, 16, 28, 40, and 52
		Percent improvement from baseline in PASI score	The percent improvement from baseline in PASI score at Weeks 2, 4, 8, 16, 28, 40, and 52
		Proportions of PASI 50/75/90/100 responders	The proportion of patients who achieve at least 50/75/90/100% improvement from baseline in PASI (PASI 50/75/90/100) at Weeks 2, 4, 8, 12, 16, 28, 40, and 52
		Proportions of Responders of sPGA score (0 or 1)	The proportion of patients with static Physician Global Assessment (sPGA) score on a 5-point scale of clear (0) or almost clear (1) at Weeks 0, 2, 4, 8, 12, 16, 28, 40, and 52
		Change in DLQI score from baseline	The change in Dermatology Life Quality Index (DLQI) score from baseline at Weeks 2, 4, 8, 12, 16, 28, 40, and 52
	Exploratory efficacy endpoints	Change from baseline of patient pain VAS for PsA	The change in patient pain VAS from baseline at Weeks 12, 16, 28, and 52 in patients with PsA

Title: A Randomised, Active-Controlled, Double-Blind, Phase 3 Study to Compare the Efficacy and Safety of CT-P43 to Stelara in Patients with Moderate to Severe Plaque Psoriasis			
Study identifier	Project code: CT-P43 EudraCT number: 2020-001045-39		
		Change from baseline of patient global assessment for PsA	The change in Patient Global Assessment VAS from baseline at Weeks 12, 16, 28, and 52 in patients with PsA
Database lock	23 Aug 2022		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Full Analysis Set (FAS): The FAS was defined as all patients who were randomly assigned and received at least 1 full dose of study drug (CT-P43 or EU-Stelara). The primary efficacy endpoint was the mean percent improvement from baseline in PASI score at Week 12 and is summarised for the FAS. The patients who administered at least one 45 mg for study drug and never received 90 mg of study drug in Treatment Period I were subject to analysis.		
Descriptive statistics and estimate variability	Treatment group	CT-P43	EU-Stelara
	Number of patients	198	194
	Least squares mean (Standard error)	78.26 (2.054)	77.33 (2.049)
	Estimate of treatment difference (%)	0.94	
	95% CI of treatment difference (%)	(-2.29, 4.16)	
Analysis description	Supportive Analysis		
Analysis population and time point description	Per-Protocol Set (PPS): The PPS was defined as all randomly assigned patients who received the full dose of study drug (CT-P43 or EU-Stelara) at Weeks 0 and 4, had a PASI assessment at baseline and Week 12, and did not have any major protocol deviation affecting the primary endpoint interpretation. Final determinations of the PPS were made at the blinded data review meeting for the efficacy primary endpoint before unblinding. The primary efficacy endpoint was the mean percent improvement from baseline in PASI score at Week 12 and is summarised for the PPS. The patients who administered at least one 45 mg for study drug and never received 90 mg of study drug in Treatment Period I were subject to analysis.		
Descriptive statistics and estimate variability	Treatment group	CT-P43	EU-Stelara
	Number of patients	195	193
	Least squares mean (Standard error)	78.41 (2.038)	77.54 (2.025)
	Estimate of treatment difference (%)	0.87	
	95% CI of treatment difference (%)	(-2.32, 4.07)	

2.3.5.3. Clinical studies in special populations

Not applicable for biosimilars.

2.3.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

See PK section 2.3.2.1.

2.3.5.6. Supportive study

Not applicable.

2.3.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Study (CT-P34 3.1) was a phase III, single randomised double-blind study designed to assess equivalence of CT-P43 to Stelara in patients with moderate to severe plaque-type psoriasis (PsO).

The selected study population of moderate to severe plaque psoriasis patients represents the most sensitive population to demonstrate biosimilarity. Additionally, ustekinumab's mechanism of action is similar in each of the reference medicinal product's indications (PsO, paediatric PsO, PsA, CD, UC) as the Th1 and Th17 cytokine pathways play a central role in their pathogenesis and are mediated by the ustekinumab targeted and inhibited IL-12 and IL-23. In addition, the safety profile for ustekinumab is similar between these indications. As such, provided similarity can be demonstrated during the stepwise approach, including quality and functional characterisation, non-clinical studies and clinical PK, it is agreed that a clinical study in PsO can be used to support extrapolation to other indications approved for Stelara.

The study comprised two periods, namely Treatment Period 1 (Week 1 to 16) during which primary efficacy was assessed, and Treatment Period 2 (Week 16 to 52) during which long-term efficacy and safety was assessed. At Week 16 (4 weeks after the primary efficacy assessment), patients initially randomised to EU-Stelara arm were re-randomised into two groups in a 1:1 ratio to either continue treatment with EU-Stelara or to switch to test. The overall study design is acceptable. The eligibility criteria were also overall acceptable. Route of administration, dosing and schedule are in line with the posology of Stelara for the treatment of PsO in subjects with BW $\geq$ 60 kg (see Stelara SmPC) and are therefore accepted. Definition of allowed and prohibited medications is adequate.

Study objectives are considered appropriate to compare the clinical efficacy, safety and tolerability, PK and immunogenicity of proposed biosimilar CT-P43 and the originator Stelara.

The mean percent improvement from baseline in the PASI score at Week 12 was chosen as the primary endpoint. This is considered sufficiently sensitive to detect potential clinically meaningful differences in efficacy. During the scientific advice (EMA/CHMP/SAWP/647848/2019), the CHMP suggested an earlier time point (e.g. week 8) would be preferred over the 12-week time point. The preference for an earlier time point was expressed in order to increase sensitivity to detect differences between treatments as the week 8 time point is at the steepest part of the curve, while at week 12 the plateau is almost reached. The mean percent improvement from baseline in PASI score at Week 8 was one of the secondary efficacy endpoints in the conducted clinical study and also endorsed during the scientific advice. The profile of the two curves for PASI score is very similar before reaching the plateau, therefore, the PASI score at Week 12 was still considered appropriate as primary endpoint.

Secondary efficacy endpoints comprised PASI 50, PASI 75, PASI 90 PASI 100, percent improvement in PASI from baseline over time, area under the effect curve for PASI from BL through Week 12, proportion of patients achieving static Physician's Global Assessment (sPGA) responses of clear (0) or almost clear (1) at all visits up to Week 52, change in Dermatology Life Quality Index (DLQI) scores from BL at different time points and change in percentage body surface area (%BSA) affected by

chronic PsO from BL to different time points up to Week 52, and are considered relevant for the overall assessment of comparability in efficacy.

Based on the information provided and the assumptions made, sample size and power calculations are acceptable.

The randomisation scheme, statistical analysis plan and analysis sets were also acceptable.

Efficacy data and additional analyses

Of the 574 patients screened, a total of 509 patients were randomly assigned to study drug (256 patients in the CT-P43 group and 253 patients in the EU-Stelara group); 65 patients had screening failure. A total of 509 patients initiated the study drug (256 [100.0%] patients in the CT-P43 group and 253 [100.0%] patients in the EU-Stelara group).

Of the 509 patients, 7 (1.4%) patients discontinued the study drug and terminated from the study (3 [1.2%] patients in the CT-P43 group and 4 [1.6%] patients in the EU-Stelara group).

The proportion of patients who discontinued the study drug and the proportion of patients who terminated from the study was generally similar between the CT-P43 and EU-Stelara groups.

The percentage of patients who completed Stage 1 at Week 16 was high and comparable between both treatment arms.

The proportion of patients with major protocol deviations was small and comparable between study arms. The most common major protocol deviations were related to receipt of prohibited medication or treatment which affect Week 12 efficacy assessment and was similar between the two treatment groups.

The study was well conducted, and the protocol deviations are unlikely to have a significant effect on the primary efficacy outcome.

Overall, demographic characteristics were well balanced and similar between the 2 groups.

The study population (demographic and baseline characteristics) is considered representative of the target population in plaque-type psoriasis.

The primary endpoint, percent change from baseline in PASI at Week 12, was equivalent between the CT-P43 and Stelara treatment groups. The adjusted difference in LS Means of the percent change from baseline in PASI at Week 12 was 0.94 and the 95% CI of the adjusted treatment difference was -2.29 to 4.16, which was entirely contained within the pre-defined equivalence margin of [-15%, 15%].

Secondary efficacy endpoints, including PASI 50, PASI 75, PASI 90, and PASI 100 response rates, were also similar between test and Stelara treatment group by visit.

The proportion of subjects achieving a PGA response 'cleared' or 'minimal' were similar between CT-P43 and Stelara treatment group by visit.

The degree of DLQI improvement was similar between CT-P43 and Stelara treatment group by visit.

The impact of ADA on efficacy was assessed in Study CT-P43 3.1. The primary efficacy endpoints are comparable regardless of ADA positivity at Week 12 and are also comparable between the CT-P43 and EU-Stelara treatment groups in both ADA positive and negative subgroups. However, the numbers who were ADA positive were very low to draw any conclusions.

Overall, it is concluded that clinical comparability has been demonstrated between CT-P43 and Stelara in the phase III clinical study based on the efficacy data provided. The efficacy outcomes are similar across primary and secondary endpoints in psoriasis patients.

The equivalence has been justified based on the interval estimates of similar historical studies. Also, from the clinical perspective it has been justified that the proposed equivalence margin of 15% can be considered not to represent a clinically relevant difference.

2.3.7. Conclusions on the clinical efficacy

Based on the data presented, CT-P43 showed similar efficacy as EU-Stelara in the primary and secondary efficacy endpoints. The equivalence of efficacy was demonstrated based on the primary endpoint and the comparable results for the secondary efficacy endpoints also supported the similarity of CT-P43 and EU-Stelara.

2.3.8. Clinical safety

Safety data for CT-P43 is based on three clinical studies, Study CT-P43 1.1, Study CT-P43 1.2 and Study CT-P43 3.1, in which safety was assessed as part of secondary study objectives.

Studies CT-P43 1.1 and CT-P43 1.2 were conducted in healthy male subjects following single dose administration, in New Zealand and Japan, respectively. Study CT-P43 3.1 was conducted in patients with PsO who received up to 5 total doses of ustekinumab. Thus, a single pooled safety analysis of the three studies was not considered meaningful and safety results are discussed below per individual study.

In clinical studies with CT-P43, all analyses of safety were conducted using the Safety Set, which is defined as all randomly assigned subjects who receive at least 1 dose (full or partial) of study drug (CT-P43, EU-Stelara or US-Stelara). Subjects were assigned to treatment groups based on the study drug actually received.

2.3.8.1. Patient exposure

In the clinical study programme of CT-P43, the Safety Set includes data from 1104 subjects in the 3 clinical studies (509 patients with moderate to severe plaque psoriasis in Study CT-P43 3.1, 270 healthy male subjects in Study CT-P43 1.1 and 325 healthy Japanese male subjects in Study CT-P43 1.2). Of these, 380 patients with moderate to severe plaque psoriasis and 205 healthy male subjects were exposed to CT-P43.

In the main clinical efficacy and safety study, Study CT-P43 3.1, patients with moderate to severe plaque psoriasis received either CT-P43 or EU-Stelara 45 mg (weight ≤ 100 kg) or 90 mg (weight > 100 kg) administered subcutaneously at Weeks 0 and 4 based on a patient's baseline body weight and at Weeks 16, 28, and 40 based on a patient's body weight at Week 16 pre-dose.

In addition, 270 healthy male subjects (all weighed ≤ 100 kg) and 325 healthy male Japanese subjects (all weighed ≤ 90 kg) received a single 45 mg dose of CT-P43, EU Stelara or US-Stelara in Studies CT-P43 1.1 and 1.2 respectively.

Table 40. Number of subjects who received at least 1 dose of study drug (ct-p43, eu-stelara or us-stelara) in ct-p43 studies (safety set)

Study	Subjects	Duration of Exposure	Number of Subjects Received ≥1 Dose of Study Drug			
			CT-P43	EU-Stelara	US-Stelara	Total
CT-P43 3.1	Moderate to severe plaque psoriasis patients	At least 1 dose	380 ¹	253	-	509
		Total 5 doses (up to Week 40)	243	121	-	364
CT-P43 1.1	Healthy male subjects	Single dose	94	98	78	270
CT-P43 1.2	Healthy Japanese male subjects	Single dose	111	108	106	325
Total		At least 1 dose	585¹	459	184	1104

¹Includes 256 patients in the CT-P43 group and 124 patients in the EU-Stelara group who underwent a transition to CT-P43 from Week 16 in Study CT-P43 3.1.

Study CT-P43 1.1: Healthy subjects

This study was conducted in two parts in 271 subjects. In Part 1, a total of 30 subjects (14 and 16 subjects in the CT-P43 and EU-Stelara groups, respectively) were randomly assigned to a treatment group and received a single dose (45 mg) of study drug. One (6.3%) subject in the EU-Stelara group discontinued from the study after the study drug administration due to withdrawal by subject.

In Part 2, a total of 241 subjects were randomly assigned to a treatment group and 240 subjects (80, 82 and 78 subjects in the CT-P43, EU-Stelara and US-Stelara groups, respectively) received a single dose (45 mg) of study drug. Of the 241 subjects, 11 (4.6%) subjects discontinued from the study (3 [3.8%], 3 [3.7%] and 5 [6.3%] subjects, respectively). Withdrawal by subject was the most frequently reported primary reason for study discontinuation (3 [3.8%], 3 [3.7%] and 4 [5.1%] subjects, respectively).

Demographics and baseline characteristics were generally similar between treatment groups. The majority of subjects were White (69.7% in total in Part 2) and non-Hispanic or Non-Latino (92.1% in total), with mean age of 29.0 years. Any slight numerical differences observed between treatment groups were not considered to be clinically relevant.

Study CT-P43 1.2: Healthy subjects

This study was conducted in Japan, with a total of 331 subjects randomly assigned to a treatment group. Of the 331 subjects, 14 (4.2%) subjects withdrew or discontinued from the study (5 [4.4%], 5 [4.5%] and 4 [3.7%] subjects in the CT-P43, EU-Stelara and US-Stelara group, respectively). Withdrawal by subject was the most frequently reported primary reason for study discontinuation (4 [3.5%], 4 [3.6%] and 3 [2.8%] subjects, respectively). Thus, 325 subjects (111, 108 and 106 subjects in the CT-P43, EU-Stelara and US-Stelara group, respectively) received a single dose (45 mg) of study drug. All subjects enrolled were Japanese males with mean age of 34.8 years and generally similar demographic and baseline characteristics across treatment groups.

Study CT-P43 3.1: Patients with moderate to severe plaque psoriasis

A total of 509 patients received study drug (45 mg or 90 mg by subcutaneous injection), with 256 patients in the CT-P43 group and with 253 patients in the EU-Stelara group. The study was conducted

in 34 centres in Estonia, Korea, Poland, and Ukraine. The majority of patients were from Poland (74.1%). Most patients were White (90.2%), the majority were male (65.6%) and the mean age of patients was 42.4 years. Demographics and baseline characteristics were generally balanced between groups.

Study drug was dosed according to weight, in line with the SmPC of reference product; patients who weighed ≤ 100 kg received 45 mg (1 injection of 45 mg/0.5 ml) of study drug by SC injection via PFS and patients who weighed >100 kg received 90 mg (2 injections of 45 mg/0.5 ml) of study drug by SC injection via PFS.

The duration of study CT-P43 3.1 was up to 58 weeks, which included Screening (up to 6 weeks), Treatment Period (up to 40 weeks), and off-dose follow-up period (12 weeks) prior to the EOS visit. For Study CT-P43 3.1, the exposure set for CT-P43 comprises 380 subjects (256 patients in the CT-P43 group and 124 patients in the EU-Stelara group who underwent a transition to CT-P43 from Week 16). The study was conducted in two treatment parts; Treatment period I from 0 to Week 16 and Treatment Period II following re-randomisation pre-week 16 dose, from Week 16 to Week 40.

For all scheduled dose up to Week 40, the proportions of patients who had total 5 doses administered were similar among the treatment groups (243 [94.9%] patients in the CT-P43 group and 242 [95.7%] patients in the EU-Stelara group). Specifically, the number of subjects receiving a total of 5 doses of CT-P43 or EU-Stelara (treatment up to Week 40) was 243 subjects receiving CT-P43 and 121 subjects receiving EU-Stelara.

Of the 509 patients randomly assigned to study drug, 7 (1.4%) patients discontinued the study drug (3 [1.2%] and 4 [1.6%] patients in the CT-P43 and EU-Stelara groups, respectively). Withdrawal by patient was the most frequently reported primary reason for study drug discontinuation (2 [0.8%] and 3 [1.2%] patients, respectively).

Table 41. Summary of patient disposition (Treatment Period II): ITT Set

Treatment Period II Subset				
	CT-P43 Maintenance (N=253)	Stelara Maintenance (N=125)	Switched to CT-P43 (N=124)	Total (N=502)
Treatment Period II	Number (%) of patients			
Randomized (2 nd)	253	125	124	502
Administered the study drug in Treatment Period II	253 (100.0%)	125 (100.0%)	124 (100.0%)	502 (100.0%)
Discontinued the study drug in Treatment Period II	10 (4.0%)	3 (2.4%)	2 (1.6%)	15 (3.0%)
Terminated the study in Treatment Period II	10 (4.0%)	3 (2.4%)	1 (0.8%)	14 (2.8%)
Completed the study ¹	239 (94.5%)	122 (97.6%)	122 (98.4%)	483 (96.2%)
Primary reason for study drug discontinuation in Treatment Period II				
Adverse event	3 (1.2%)	1 (0.8%)	1 (0.8%)	5 (1.0%)
Lost to follow-up	1 (0.4%)	0	0	1 (0.2%)
Death	1 (0.4%)	0	0	1 (0.2%)
Withdrawal by patient	5 (2.0%)	2 (1.6%)	1 (0.8%)	8 (1.6%)
Time on study drug prior to discontinuation in Treatment Period II (days) ²				
n	10	3	2	15
Mean	172.9	141.0	204.5	170.7
SD	40.75	54.67	10.61	43.11
Minimum	110	106	197	106
Median	197.0	113.0	204.5	197.0
Maximum	202	204	212	212
Primary reason for study termination in Treatment Period II				
Withdrawal by patient	7 (2.8%)	3 (2.4%)	1 (0.8%)	11 (2.2%)
Lost to follow-up	2 (0.8%)	0	0	2 (0.4%)
Death	1 (0.4%)	0	0	1 (0.2%)

Abbreviations: ITT, intent-to-treat; SD, standard deviation.

- Completed the study: Counted as patients who treated study drug answered 'Yes' to both questions for completion of the study drug administration on 'Study Drug Discontinuation' and completion of EOS visit on 'Study Termination' eCRF pages.
- Only for patients who initiated the study drug during each treatment period and prematurely discontinued study drug calculated as (date of last administration – date of first administration + 1).

2.3.8.2. Adverse events

Study CT-P43 1.1 Part 1

In the Safety Set of Part 1, 26 (86.7%) subjects (13 [92.9%] subjects in the CT-P43 treatment group and 13 [81.3%] subjects in the EU- Stelara treatment group) experienced at least 1 TEAE. The most frequently reported TEAE in Part 1, regardless of relationship to study drug, was headache (3 [21.4%] subjects in the CT-P43 treatment group and 5 [31.3%] subjects in the EU- Stelara treatment group). The second most frequently reported TEAE was upper respiratory tract infection (3 [21.4%] subjects in the CT-P43 treatment group and 3 [18.8%] subjects in the EU-approved Stelara treatment group) followed by oropharyngeal pain (1 [7.1%] subject in the CT-P43 treatment group and 3 [18.8%] subjects in the EU- Stelara treatment group).

Table 42. Summary of TEAEs (Reported for ≥2 Subjects by PT in Any Treatment Group) by SOC and PT in Study CT-P43 1.1–Part 1 (Safety Set)

Preferred Term ^(a) , n (%)	CT-P43 (N=14)	EU-approved	Total (N=30)
		Stelara (N=16)	
Headache	3 (21.4)	5 (31.3)	8 (26.7)
Upper respiratory tract infection	3 (21.4)	3 (18.8)	6 (20.0)
Oropharyngeal pain	1 (7.1)	3 (18.8)	4 (13.3)
Injection site reaction	2 (14.3)	1 (6.3)	3 (10.0)
Muscle strain	1 (7.1)	2 (12.5)	3 (10.0)
Nasal congestion	0	3 (18.8)	3 (10.0)
Pain in extremity	0	2 (12.5)	2 (6.7)
Skin laceration	0	2 (12.5)	2 (6.7)

Abbreviations: EU, European Union; TEAE, treatment-emergent adverse event.

Note: The total number of TEAEs count includes events for subjects in the Safety Set. A subject with 2 or more TEAEs within the same preferred term is counted only once using the most severe intensity. Preferred terms were arranged by decreasing total percentage.

^(a) Coded from Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0.

In Part 1, TEAEs considered related to the study drug by the investigator were reported in 5 (35.7%) and 8 (50.0%) subjects in the CT-P43 and EU-Stelara groups, respectively. The most frequently reported TEAE considered related to the study drug by the investigator was injection site reaction (2 [14.3%] and 1 [6.3%] subjects, respectively) and upper respiratory tract infection (1 [7.1%] and 2 [12.5%] subjects, respectively). All of the TEAEs, regardless of relationship to study drug, were grade 1 or grade 2 in intensity.

Study CT-P43 1.1 Part 2

In the Safety Set of Part 2, 195 (81.3%) subjects (68 [85.0%] subjects in the CT-P43 treatment group, 63 [76.8%] subjects in the EU- Stelara treatment group, and 64 [82.1%] subjects in the US Stelara treatment group) experienced at least 1 TEAE. Treatment-emergent AEs considered related to the study drug by the investigator were reported in 80 (33.3%) subjects (25 [31.3%] subjects in the CT-P43 treatment group, 28 [34.1%] subjects in the EU-approved Stelara treatment group, and 27 [34.6%] subjects in the US-licensed Stelara treatment group).

Table 43. Summary of adverse events – Part 2 (safety set)

	CT-P43 (N=80)	EU-approved Stelara (N=82)	US-licensed Stelara (N=78)	Total (N=240)
Total number of AEs	196	190	166	552
Total number of TEAEs	189	180	159	528
Number of Subjects with at Least 1, n (%)	68 (85.0)	63 (76.8)	64 (82.1)	195 (81.3)
Related to the study drug	25 (31.3)	28 (34.1)	27 (34.6)	80 (33.3)
Unrelated to the study drug	64 (80.0)	57 (69.5)	56 (71.8)	177 (73.8)
Total number of TESAEs	2	0	2	4
Number of Subjects with at Least 1, n (%)	2 (2.5)	0	2 (2.6)	4 (1.7)
Related to the study drug	1 (1.3)	0	0	1 (0.4)
Unrelated to the study drug	1 (1.3)	0	2 (2.6)	3 (1.3)
TEAE leading to study discontinuation	0	0	0	0
TEAE leading to death	0	0	0	0
Total number of TEAE classified as hypersensitivity reaction	1	1	0	2
Number of Subjects with at Least 1, n (%)	1 (1.3)	1 (1.2)	0	2 (0.8)
Total number of TEAE classified as injection site reaction	9	9	7	25
Number of Subjects with at Least 1, n (%)	9 (11.3)	9 (11.0)	7 (9.0)	25 (10.4)
Total number of TEAE classified as infection	27	34	28	89
Number of Subjects with at Least 1, n (%)	22 (27.5)	25 (30.5)	24 (30.8)	71 (29.6)
Related to the study drug	4 (5.0)	9 (11.0)	5 (6.4)	18 (7.5)
Unrelated to the study drug	20 (25.0)	19 (23.2)	21 (26.9)	60 (25.0)
TEAE classified as serious infection	0	0	0	0
TEAE classified as malignancy	0	0	0	0

Abbreviations: AE, adverse event; EU, European Union; TEAE, treatment-emergent adverse event; TESA, treatment-emergent serious adverse event; US, United States.

Note: The total number of TEAEs count includes events for subjects in the safety set. The event is considered to be related if the relationship is defined as 'possible', 'probable' or 'definite'. A subject with 2 or more TEAEs within the same SOC, PT, and relationship is counted only once using the most severe intensity.

The most frequently reported TEAE in Part 2, regardless of relationship to study drug, was upper respiratory tract infection (12 [15.0%] subjects in the CT-P43 treatment group, 20 [24.4%] subjects in the EU- Stelara treatment group, and 19 [24.4%] subjects in the US- Stelara treatment group). The second most frequently reported TEAE was headache (17 [21.3%] subjects in the CT-P43 treatment group, 14 [17.1%] subjects in the EU- Stelara treatment group, and 11 [14.1%] subjects in the US- Stelara treatment group) followed by injection site reaction (9 [11.3%] subjects in the CT-P43 treatment group, 9 [11.0%] subjects in the EU- Stelara treatment group, and 7 [9.0%] subjects in the US- Stelara treatment group) and skin abrasion (8 [10.0%] subjects in the CT-P43 treatment group, 10 [12.2%] subjects in the EU- Stelara treatment group, and 6 [7.7%] subjects in the US- Stelara treatment group). All other TEAEs were reported by less than 10% of subjects overall.

Table 44. Summary of TEAEs (Reported for ≥3% of Subjects by PT in Any Treatment Group) by SOC and PT in Study CT-P43 1.1–Part 2 (Safety Set)

SOC PT	CT-P43 (N=80)	EU-Stelara (N=82)	US-Stelara (N=78)
Total Number of TEAEs	189	180	159
Number (%) of subjects with at least 1 TEAE	68 (85.0)	63 (76.8)	64 (82.1)
Related	25 (31.3)	28 (34.1)	27 (34.6)
Unrelated	64 (80.0)	57 (69.5)	56 (71.8)
Cardiac disorders	4 (5.0)	1 (1.2)	1 (1.3)
Palpitations	3 (3.8)	1 (1.2)	1 (1.3)
Gastrointestinal disorders	13 (16.3)	13 (15.9)	11 (14.1)
Diarrhoea	2 (2.5)	4 (4.9)	2 (2.6)
Nausea	5 (6.3)	2 (2.4)	2 (2.6)
Toothache	1 (1.3)	1 (1.2)	3 (3.8)
Vomiting	3 (3.8)	1 (1.2)	0
General disorders and administration site conditions	21 (26.3)	22 (26.8)	18 (23.1)
Fatigue	4 (5.0)	4 (4.9)	5 (6.4)
Injection site reaction	9 (11.3)	9 (11.0)	7 (9.0)
Vessel puncture site bruise	7 (8.8)	3 (3.7)	3 (3.8)
Immune system disorders	4 (5.0)	2 (2.4)	0
Seasonal allergy	3 (3.8)	1 (1.2)	0
Infections and infestations	22 (27.5)	25 (30.5)	24 (30.8)
Gastroenteritis	4 (5.0)	7 (8.5)	1 (1.3)
Upper respiratory tract infection	12 (15.0)	20 (24.4)	19 (24.4)
Injury, poisoning and procedural complications	27 (33.8)	28 (34.1)	19 (24.4)
Contusion	2 (2.5)	5 (6.1)	3 (3.8)
Ligament sprain	5 (6.3)	4 (4.9)	3 (3.8)
Muscle strain	2 (2.5)	4 (4.9)	1 (1.3)
Skin abrasion	8 (10.0)	10 (12.2)	6 (7.7)
Skin laceration	7 (8.8)	2 (2.4)	5 (6.4)
Sunburn	3 (3.8)	4 (4.9)	1 (1.3)
Musculoskeletal and connective tissue disorders	11 (13.8)	7 (8.5)	9 (11.5)
Arthralgia	3 (3.8)	0	1 (1.3)
Back pain	4 (5.0)	1 (1.2)	2 (2.6)
Nervous system disorders	19 (23.8)	18 (22.0)	13 (16.7)
Headache	17 (21.3)	14 (17.1)	11 (14.1)
Respiratory, thoracic and mediastinal disorders	14 (17.5)	9 (11.0)	23 (29.5)
Cough	5 (6.3)	3 (3.7)	1 (1.3)
Nasal congestion	1 (1.3)	2 (2.4)	4 (5.1)
Oropharyngeal pain	6 (7.5)	1 (1.2)	3 (3.8)
Rhinorrhoea	1 (1.3)	2 (2.4)	4 (5.1)

SOC PT	CT-P43 (N=80)	EU-Stelara (N=82)	US-Stelara (N=78)
-----------	------------------	----------------------	----------------------

Note: Only TEAEs reported for at least 3% of patients by PT in any treatment group were included. A subject with 2 or more TEAEs within the same system organ class, and preferred term is counted only once. System organ classes and preferred terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary, Version 23.0.

Abbreviations: EU, European Union; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event; US, United States.

In the Safety Set of Part 2, most of the TEAEs, regardless of relationship to study drug, were grade 1 or grade 2 in intensity. Four (1.7%) subjects (1 [1.3%] subjects in the CT-P43 treatment group, 1 [1.2%] subjects in the EU- Stelara treatment group, and 2 [2.6%] subjects in the US- Stelara treatment group) experienced at least 1 grade 3 TEAE.

Table 45. Summary of TEAEs by Intensity of Grade 3 or Higher in Study CT-P43 1.1 Part 2 (Safety Set)

SOC PT	CT-P43 (N=80)	EU-Stelara (N=82)	US-Stelara (N=78)
Number (%) of subjects with at least 1 TEAE of grade 3 or higher	1 (1.3)	1 (1.2)	3 (3.8)
Grade 3	1 (1.3)	1 (1.2)	2 (2.6)
Grade 4	0	0	1 (1.3)
Grade 3 or higher TEAEs by SOC/PT			
Injury, poisoning and procedural complications	1 (1.3)	1 (1.2)	2 (2.6)
Clavicle fracture	0	1 (1.2)	1 (1.3)
Neck injury	0	0	1 (1.3)
Skin laceration	1 (1.3)	0	0
Investigations	0	0	1 (1.3)
Blood creatine phosphokinase increased	0	0	1 (1.3)

Study CT-P43 1.2

A total of 260 TEAEs were reported in 163 (50.2%) subjects (61 [55.0%] subjects in the CT-P43 treatment arm, 54 [50.0%] subjects in the EU- Stelara treatment arm, and 48 [45.3%] subjects in the US- Stelara treatment arm).

Treatment-emergent AEs considered related to the study drug by the investigator were reported for 108 (33.2%) subjects (41 [36.9%] subjects in the CT-P43 treatment arm, 38 [35.2%] subjects in the EU- Stelara treatment arm, and 29 [27.4%] subjects in the US- Stelara treatment arm).

Table 46. Summary of adverse events (Safety set)

	CT-P43 (N=111)	EU-approved Stelara (N=108)	US-licensed Stelara (N=106)	Total (N=325)
Total number of AEs	87	95	79	261
Total number of TEAEs	87	94	79	260
Number of Subjects with at Least 1, n (%)	61 (55.0)	54 (50.0)	48 (45.3)	163 (50.2)
Related to the study drug	41 (36.9)	38 (35.2)	29 (27.4)	108 (33.2)
Unrelated to the study drug	27 (24.3)	26 (24.1)	28 (26.4)	81 (24.9)
Total number of TESAEs	0	0	0	0
Total number of TEAE leading to study discontinuation	0	0	0	0
Total number of TEAE leading to death	0	0	0	0
Total number of TEAE classified as hypersensitivity reaction	0	1	0	1
Number of Subjects with at Least 1, n (%)	0	1 (0.9)	0	1 (0.3)
Related to the study drug	0	1 (0.9)	0	1 (0.3)
Total number of TEAE classified as injection site reaction	22	14	10	46
Number of Subjects with at Least 1, n (%)	22 (19.8)	14 (13.0)	10 (9.4)	46 (14.2)
Related to the study drug	22 (19.8)	14 (13.0)	10 (9.4)	46 (14.2)
Total number of TEAE classified as infection	21	17	17	55
Number of Subjects with at Least 1, n (%)	18 (16.2)	16 (14.8)	17 (16.0)	51 (15.7)
Related to the study drug	11 (9.9)	12 (11.1)	11 (10.4)	34 (10.5)
Unrelated to the study drug	8 (7.2)	4 (3.7)	6 (5.7)	18 (5.5)
Total number of TEAE classified as serious infection	0	0	0	0
Total number of TEAE classified as malignancy	0	0	0	0
Total number of TEAE classified as adverse device effect	0	0	0	0

Abbreviations: AE, adverse event; EU, European Union; TEAE, treatment-emergent adverse event; TESA, treatment-emergent serious adverse event; US, United States.

Note: The total number of TEAEs count includes events for subjects in the safety set. The event is considered to be related if the relationship is defined as 'possible', 'probable' or 'definite'. A subject with 2 or more TEAEs within the same SOC, PT, and relationship is counted only once.

Table 47. Treatment-emergent adverse events reported for $\geq 3\%$ of subjects in either treatment arm by preferred term (safety set)

Preferred Term ^(a) , n (%)	CT-P43 (N=111)	EU-approved Stelara (N=108)	US-licensed Stelara (N=106)	Total (N=325)
Injection site reaction	22 (19.8)	14 (13.0)	10 (9.4)	46 (14.2)
Nasopharyngitis	4 (3.6)	8 (7.4)	9 (8.5)	21 (6.5)
COVID-19	9 (8.1)	5 (4.6)	4 (3.8)	18 (5.5)
Blood creatine phosphokinase increased	8 (7.2)	5 (4.6)	4 (3.8)	17 (5.2)
Alanine aminotransferase increased	3 (2.7)	4 (3.7)	6 (5.7)	13 (4.0)
Myalgia	2 (1.8)	5 (4.6)	1 (0.9)	8 (2.5)
C-reactive protein increased	4 (3.6)	0	1 (0.9)	5 (1.5)

Abbreviations: EU, European Union; TEAE, treatment-emergent adverse event; US, United States.

Note: A subject with 2 or more TEAEs within the same preferred term is counted only once. Preferred terms were arranged by decreasing total percentage.

^(a) Coded from Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1.

In the Safety Set, most of the TEAEs, regardless of relationship to study drug, were grade 1 or grade 2 in intensity. Overall, 8 (2.5%) subjects (4 [3.6%] subjects in the CT-P43 treatment arm, 2 [1.9%] subjects each in the EU-approved Stelara and US-licensed Stelara treatment arm) experienced at least 1 grade 3 TEAE as the most severe grade and 4 (1.2%) subjects (1 [0.9%] subject each in the CT-P43 and US-licensed Stelara treatment arm, and 2 [1.9%] subjects in the EU-approved Stelara treatment arm) experienced at least 1 grade 4 TEAE as the most severe grade.

All grade 3 or higher reported TEAEs were laboratory parameters in the SOC of investigations, which were all unrelated with the study drug and all subjects were recovered from the event without any treatments given, except for 1 subject in the EU-approved Stelara treatment arm who experienced a non-serious TEAE of blood CPK increased on Day 85 which was unrelated to the study drug, considered by investigator due to the subject's winter sports and travel and no treatments were given.

Table 48. Summary of TEAEs by Intensity of Grade 3 or Higher in Study CT-P43 1.2 (Safety Set)

SOC PT	CT-P43 (N=111)	EU-Stelara (N=108)	US-Stelara (N=106)
Number (%) of subjects with at least 1 TEAE of grade 3 or higher	5 (4.5)	4 (3.7)	3 (2.8)
Grade 3	4 (3.6)	2 (1.9)	2 (1.9)
Grade 4	1 (0.9)	2 (1.9)	1 (0.9)
Grade 3 or higher TEAEs by SOC/PT			
Investigations	5 (4.5)	4 (3.7)	3 (2.8)
Blood creatine phosphokinase increased	3 (2.7)	2 (1.9)	3 (2.8)
Blood triglycerides increased	2 (1.8)	2 (1.9)	0

Phase III Study CT-P43 3.1

Treatment period I

Overall, 268 TEAEs were reported in 170 (33.4%) patients (95 [37.1%] patients and 75 [29.6%] patients in the CT-P43 group and EU-Stelara group, respectively). The majority of TEAEs were Grade 1 or 2 in intensity.

In the Treatment Period I, TEAEs considered by the investigator to be related to the study drug were reported for 18 (7.0%) and 15 (5.9%) patients in the CT-P43 and EU-Stelara groups, respectively. The most frequently reported related TEAEs by PT were injection site reaction (3 [1.2%] and 2 [0.8%] patients, respectively) and COVID-19 (1 [0.4%] and 4 [1.6%] patients, respectively).

Based on PT, no TEAE considered by the investigator to be related to the study drug was reported for at least 3% of patients in either group.

Table 49. Summary of Treatment-Emergent Adverse Events (Treatment Period I): Safety Set

	CT-P43 (N=256)	Stelara (N=253)	Total (N=509)
Total number of TEAEs	158	110	268
Number (%) of patients with at least 1 TEAE	95 (37.1%)	75 (29.6%)	170 (33.4%)
Related to the study drug	18 (7.0%)	15 (5.9%)	33 (6.5%)
Unrelated to the study drug	82 (32.0%)	65 (25.7%)	147 (28.9%)
Total number of TESAEs	4	4	8
Number (%) of patients with at least 1 TESA	4 (1.6%)	4 (1.6%)	8 (1.6%)
Related to the study drug	1 (0.4%)	0	1 (0.2%)
Unrelated to the study drug	3 (1.2%)	4 (1.6%)	7 (1.4%)
Total number of TEAEs leading to discontinuation of study drug	0	0	0
Total number of TEAEs classified as infections	39	35	74
Number (%) of patients with at least 1 TEAE classified as infections	34 (13.3%)	32 (12.6%)	66 (13.0%)
Related to the study drug	9 (3.5%)	8 (3.2%)	17 (3.3%)
Unrelated to the study drug	25 (9.8%)	25 (9.9%)	50 (9.8%)
Total number of TEAEs classified as injection site reactions	3	2	5
Number (%) of patients with at least 1 TEAE classified as injection site reactions	3 (1.2%)	2 (0.8%)	5 (1.0%)
Related to the study drug	3 (1.2%)	2 (0.8%)	5 (1.0%)
Unrelated to the study drug	0	0	0
Total number of TEAEs classified as hypersensitivity reactions	0	0	0
Total number of TEAEs classified as malignancies	0	0	0
Total number of TEAEs leading to death	0	0	0

Abbreviations: TEAE, treatment-emergent adverse event; TESA, treatment-emergent serious adverse event.

Note: The total number of TEAEs counted included events of all patients in the Safety Set. At each level of summarization, a patient was counted once if they reported 1 or more events. The event was considered to be related if the relationship was defined as "possible," "probable," or "definite."

The majority of TEAEs were CTCAE Grade 1 or 2 in intensity. Overall, 21 (4.1%) patients (12 [4.7%] patients in the CT-P43 group and 9 [3.6%] patients in the EU-Stelara group) experienced at least 1 Grade 3 TEAE, and 7 (1.4%) patients (3 [1.2%] patients in the CT-P43 group and 4 [1.6%] patients in the EU-Stelara group) experienced at least 1 Grade 4 TEAE.

For Grade 3, the most frequently reported TEAEs were neutropenia and hypertriglyceridaemia. Grade 3 neutropenia was reported for 5 (1.0%) patients (2 [0.8%] patients in the CT-P43 group and 3 [1.2%] patients in the EU-Stelara group) and Grade 3 hypertriglyceridaemia was reported for 5 (1.0%) patients (3 [1.2%] patients in the CT-P43 group and 2 [0.8%] patients in the EU Stelara group).

For Grade 4, the most frequently reported TEAE was neutropenia reported for 3 (0.6%) patients (2 [0.8%] patients in the CT-P43 group and 1 [0.4%] patient in the EU-Stelara group). No Grade 5 TEAEs were reported in any group.

Treatment Period II and Follow-up Period (up to EOS)

Overall, 326 TEAEs were reported in 189 (37.6%) patients (86 [34.0%], 51 [40.8%], and 52 [41.9%] patients in the CT-P43 maintenance, EU-Stelara maintenance and switched to CT-P43 groups, respectively). The majority of TEAEs were Grade 1 or 2 in intensity.

The proportions of patients who experienced at least 1 TEAE considered by the investigator to be related to the study drug was similar among the 3 groups (14 [5.5%], 8 [6.4%], and 12 [9.7%] patients in the CT-P43 maintenance, EU-Stelara maintenance, and switched to CT-P43 groups, respectively).

Based on PT, alanine aminotransferase increased (no patients in the CT-P43 maintenance and EU-Stelara maintenance groups, and 4 [3.2%] patients in the Switched to CT-P43 group) was the only TEAE considered by the investigator to be related to the study drug reported for at least 3% of patients in any of the groups. All patients experienced the related PT ALT increased with grade 1 or 2 in intensity, except 1 (0.8%) related non-serious grade 3 intensity TEAE of ALT increased in the Switched to CT-P43 group. The patient was recovered from the TEAE.

Table 50. Overview of TEAEs in Study CT-P43 3.1 (Patients with moderate to severe plaque psoriasis): Safety Set/Safety- Treatment Period II Subset

	Study CT-P43 3.1 (Patients with moderate to severe plaque psoriasis)						
	Treatment Period I (up to Week 16)		Treatment Period II and Follow-up Period (from Week 16 up to EOS)		Overall Period (up to EOS)		
	CT-P43 (N=256)	EU-Stelara (N=253)	EU-Stelara Maintenance (N=125)	Switched to CT-P43 (N=124)	CT-P43 (N=256)	EU-Stelara Overall (N=253)	EU-Stelara Maintenance (N=125)
Total number of TEAEs	158	110	83	100	301	293	127
Number (%) of patients with ≥ 1 TEAE	95 (37.1)	75 (29.6)	51 (40.8)	52 (41.9)	137 (53.5)	140 (55.3)	64 (51.2)
Number (%) of patients with ≥ 1 Related TEAE	18 (7.0)	15 (5.9)	8 (6.4)	12 (9.7)	27 (10.5)	33 (13.0)	13 (10.4)
Number (%) of patients with ≥ 1 TEAE leading to death	0	0	0	0	1 (0.4)	0	0
Number (%) of patients with ≥ 1 TESAE	4 (1.6)	4 (1.6)	3 (2.4)	2 (1.6)	9 (3.5)	8 (3.2)	5 (4.0)
Number (%) of patients with ≥ 1 TEAE leading to study drug discontinuation	0	0	1 (0.8)	1 (0.8)	5 (2.0)	2 (0.8)	1 (0.8)
Number (%) of patients with ≥ 1 TEAE of hypersensitivity reactions	0	0	0	0	1 (0.4)	0	0
Number (%) of patients with ≥ 1 TEAE of injection site reactions	3 (1.2)	2 (0.8)	0	2 (1.6)	4 (1.6)	4 (1.6)	0
Number (%) of patients with ≥ 1 TEAE of infection/serious infection	34 (13.3)	32 (12.6)	23 (18.4)	24 (19.4)	67 (26.2)	74 (29.2)	33 (26.4)
Number (%) of patients with ≥ 1 TEAE of malignancy	0	0	0	0	1 (0.4)	0	0
Sources: [REDACTED]							
Note: At each level of summarization, subjects are counted once if they reported 1 or more events							
When the causal relationship with the study drug was judged to be "Possible" "Probable" or "Definite" it was considered that the relationship with cannot be ruled out.							
Abbreviations: EOS, End-of-Study; EU, European Union; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse							

Table 51. Summary of Treatment-Emergent Adverse Events (Treatment Period II and up to EOS): Safety – Treatment Period II Subset

	CT-P43 Maintenance (N=253)	Stelara Maintenance (N=125)	Switched to CT-P43 (N=124)	Total (N=502)
Total number of TEAEs	143	83	100	326
Number (%) of patients with at least 1 TEAE	86 (34.0%)	51 (40.8%)	52 (41.9%)	189 (37.6%)
Related to the study drug	14 (5.5%)	8 (6.4%)	12 (9.7%)	34 (6.8%)
Unrelated to the study drug	75 (29.6%)	46 (36.8%)	45 (36.3%)	166 (33.1%)
Total number of TSEAEs	5	3	2	10
Number (%) of patients with at least 1 TSEAE	5 (2.0%)	3 (2.4%)	2 (1.6%)	10 (2.0%)
Related to the study drug	1 (0.4%)	0	0	1 (0.2%)
Unrelated to the study drug	4 (1.6%)	3 (2.4%)	2 (1.6%)	9 (1.8%)
Total number of TEAEs leading to discontinuation of study drug	5	1	1	7
Number (%) of patients with at least 1 TEAE leading to discontinuation of study drug	5 (2.0%)	1 (0.8%)	1 (0.8%)	7 (1.4%)
Related to the study drug	1 (0.4%)	1 (0.8%)	0	2 (0.4%)
Unrelated to the study drug	4 (1.6%)	0	1 (0.8%)	5 (1.0%)
Total number of TEAEs classified as infections	41	28	30	99
Number (%) of patients with at least 1 TEAE classified as infection	39 (15.4%)	23 (18.4%)	24 (19.4%)	86 (17.1%)
Related to the study drug	7 (2.8%)	5 (4.0%)	5 (4.0%)	17 (3.4%)
Unrelated to the study drug	33 (13.0%)	18 (14.4%)	19 (15.3%)	70 (13.9%)
Total number of TEAEs classified as injection site reactions	1	0	2	3
Number (%) of patients with at least 1 TEAE classified as injection site reactions	1 (0.4%)	0	2 (1.6%)	3 (0.6%)
Related to the study drug	0	0	2 (1.6%)	2 (0.4%)

	CT-P43 Maintenance (N=253)	Stelara Maintenance (N=125)	Switched to CT-P43 (N=124)	Total (N=502)
Unrelated to the study drug	1 (0.4%)	0	0	1 (0.2%)
Total number of TEAEs classified as hypersensitivity reactions	1	0	0	1
Number (%) of patients with at least 1 TEAE classified as hypersensitivity reactions	1 (0.4%)	0	0	1 (0.2%)
Related to the study drug	1 (0.4%)	0	0	1 (0.2%)
Unrelated to the study drug	0	0	0	0
Total number of TEAEs classified as malignancies	1	0	0	1
Number (%) of patients with at least 1 TEAE classified as malignancies	1 (0.4%)	0	0	1 (0.2%)
Related to the study drug	1 (0.4%)	0	0	1 (0.2%)
Unrelated to the study drug	0	0	0	0
Total number of TEAEs leading to death	1	0	0	1
Number (%) of patients with TEAEs leading to death	1 (0.4%)	0	0	1 (0.2%)
Related to the study drug	0	0	0	0
Unrelated to the study drug	1 (0.4%)	0	0	1 (0.2%)

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

Note: The total number of TEAEs counted included all patient events. At each level of summarization, a patient was counted once if they reported 1 or more events. The event was considered to be related if the relationship was defined as "possible," "probable," or "definite."

Table 52. Summary of TEAEs (Reported for ≥3% of Patients by PT in Any Treatment Group) by SOC and PT in Study CT-P43 3.1 (Safety Set/Safety-Treatment Period II Subset)

SOC PT	Treatment Period I (up to Week 16)		Treatment Period II and Follow-up Period (from Week 16 up to EOS)		Overall Period (up to EOS)			
	CT-P43 (N=256)	EU-Stelara (N=253)	EU-Stelara Maintenance (N=125)	Switched to CT-P43 (N=124)	CT-P43 (N=256)	EU-Stelara		
						Overall (N=253)	EU-Stelara Maintenance (N=125)	Switched to CT-P43 (N=124)
Total Number of TEAEs	158	110	83	100	301	293	127	163
Number (%) of patients with at least 1 TEAE	95 (37.1)	75 (29.6)	51 (40.8)	52 (41.9)	137 (53.5)	140 (55.3)	64 (51.2)	75 (60.5)
Related	18 (7.0)	15 (5.9)	8 (6.4)	12 (9.7)	27 (10.5)	33 (13.0)	13 (10.4)	20 (16.1)
Unrelated	82 (32.0)	65 (25.7)	46 (36.8)	45 (36.3)	121 (47.3)	123 (48.6)	56 (44.8)	66 (53.2)
Blood and lymphatic system disorder	4 (1.6)	6 (2.4)	3 (2.4)	4 (3.2)	6 (2.3)	12 (4.7)	7 (5.6)	5 (4.0)
Neutropenia	4 (1.6)	4 (1.6)	2 (1.6)	2 (1.6)	4 (1.6)	7 (2.8)	4 (3.2)	3 (2.4)
General disorders and administration site conditions	12 (4.7)	10 (4.0)	5 (4.0)	2 (1.6)	16 (6.3)	15 (5.9)	6 (4.8)	9 (7.3)
Injection site reaction	3 (1.2)	2 (0.8)	0	2 (1.6)	4 (1.6)	4 (1.6)	0	4 (3.2)
Vaccination site pain	5 (2.0)	6 (2.4)	2 (1.6)	0	6 (2.3)	6 (2.4)	2 (1.6)	4 (3.2)
Infections and infestations	34 (13.3)	32 (12.6)	23 (18.4)	24 (19.4)	67 (26.2)	74 (29.2)	33 (26.4)	41 (33.1)
COVID-19	11 (4.3)	12 (4.7)	11 (8.8)	7 (5.6)	24 (9.4)	29 (11.5)	16 (12.8)	13 (10.5)
Latent tuberculosis	0	0	4 (3.2)	4 (3.2)	7 (2.7)	8 (3.2)	4 (3.2)	4 (3.2)
Nasopharyngitis	2 (0.8)	1 (0.4)	1 (0.8)	4 (3.2)	3 (1.2)	6 (2.4)	2 (1.6)	4 (3.2)
Upper respiratory tract infection	3 (1.2)	8 (3.2)	4 (3.2)	7 (5.6)	13 (5.1)	18 (7.1)	5 (4.0)	13 (10.5)

Investigations	12 (4.7)	14 (5.5)	16 (12.8)	17 (13.7)	29 (11.3)	42 (16.6)	19 (15.2)	22 (17.7)
Alanine aminotransferase increased	5 (2.0)	4 (1.6)	3 (2.4)	6 (4.8)	8 (3.1)	12 (4.7)	5 (4.0)	7 (5.6)
Aspartate aminotransferase increased	3 (1.2)	0	3 (2.4)	4 (3.2)	5 (2.0)	7 (2.8)	3 (2.4)	4 (3.2)
Neutrophil count decreased	0	1 (0.4)	2 (1.6)	3 (2.4)	1 (0.4)	6 (2.4)	2 (1.6)	4 (3.2)
White blood cell count decreased	1 (0.4)	1 (0.4)	3 (2.4)	3 (2.4)	5 (2.0)	7 (2.8)	3 (2.4)	4 (3.2)
Metabolism and nutrition disorders	12 (4.7)	4 (1.6)	2 (1.6)	5 (4.0)	17 (6.6)	11 (4.3)	4 (3.2)	7 (5.6)
Hypertriglyceridaemia	4 (1.6)	2 (0.8)	1 (0.8)	4 (3.2)	7 (2.7)	7 (2.8)	1 (0.8)	6 (4.8)
Nervous system disorders	7 (2.7)	7 (2.8)	2 (1.6)	2 (1.6)	13 (5.1)	11 (4.3)	2 (1.6)	9 (7.3)
Headache	6 (2.3)	4 (1.6)	1 (0.8)	1 (0.8)	10 (3.9)	6 (2.4)	1 (0.8)	5 (4.0)
Vascular disorders	7 (2.7)	1 (0.4)	2 (1.6)	2 (1.6)	9 (3.5)	5 (2.0)	2 (1.6)	3 (2.4)
Hypertension	7 (2.7)	1 (0.4)	2 (1.6)	2 (1.6)	9 (3.5)	5 (2.0)	2 (1.6)	3 (2.4)

Sources:

Note: Only PTs reported for at least 3% of patients in any treatment group were included in this table. At each level of summarization, patients are counted once if they reported one or more events. System organ classes and preferred terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary, Version 24.1.

Abbreviations: COVID-19, Coronavirus Disease 2019; EOS, End-of-Study; EU, European Union; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

The majority of TEAEs were CTCAE Grade 1 or 2 in intensity. Overall, 23 (4.6%) patients (10 [4.0%], 6 [4.8%], and 7 [5.6%] patients in the CT-P43 maintenance, EU-Stelara maintenance, and Switched to CT-P43 groups, respectively) experienced at least 1 Grade 3 TEAE, and 3 (0.6%) patients (none in the CT-P43 maintenance, 1 [0.8%] patient in the EU-Stelara maintenance, and 2 [1.6%] patients in the Switched to CT-P43 groups, respectively) experienced at least 1 Grade 4 TEAE, and 1 (0.2%) patient in the CTP43 maintenance group experienced Grade 5 TEAE.

For Grade 3, the most frequently reported TEAE was hypertriglyceridaemia for 3 (0.6%) patients (all considered unrelated) (2 [0.8%], 1 [0.8%], and no patients in the CT-P43 maintenance, EU-Stelara maintenance, and Switched to CT-P43 groups, respectively).

For Grade 4, the most frequently reported TEAE was neutrophil count decreased for 2 (0.4%) patients (none, 1 [0.8%], and 1 [0.8%] patients in the CT-P43 maintenance, EU-Stelara maintenance, and Switched to CT-P43 groups, respectively).

Except for 1 TEAE of myocardial infarction considered unrelated to study drug in 1 (0.4%) patient in the CT-P43 maintenance group, no Grade 5 TEAEs were reported in any group.

Table 53. Summary of TEAEs by Intensity of Grade 3 or Higher in Study CT-P43 3.1 (Safety Set/Safety-Treatment Period II Subset)

SOC PT	Treatment Period I (up to Week 16)		Treatment Period II and Follow-up Period (from Week 16 up to EOS)		Overall Period (up to EOS)			
	CT-P43 (N=256)	EU-Stelara (N=253)	EU-Stelara Maintenance (N=125)	Switched to CT-P43 (N=124)	CT-P43 (N=256)	EU-Stelara		
						Overall (N=253)	EU-Stelara Maintenance (N=125)	Switched to CT-P43 (N=124)
Number (%) of patients with at least 1 TEAE of grade 3 or higher	15 (5.9)	13 (5.1)	7 (5.6)	9 (7.3)	24 (9.4)	25 (9.9)	11 (8.8)	13 (10.5)
Grade 3	12 (4.7)	9 (3.6)	6 (4.8)	7 (5.6)	20 (7.8)	19 (7.5)	9 (7.2)	10 (8.1)
Grade 4	3 (1.2)	4 (1.6)	1 (0.8)	2 (1.6)	3 (1.2)	6 (2.4)	2 (1.6)	3 (2.4)
Grade 5	0	0	0	0	1 (0.4)	0	0	0
Grade 3 or higher TEAEs by SOC/PT (reported for ≥ 1% of patients by PT in any treatment group)								
Blood and lymphatic system disorders	4 (1.6)	4 (1.6)	2 (1.6)	1 (0.8)	4 (1.6)	6 (2.4)	4 (3.2)	2 (1.6)
Neutropenia	4 (1.6)	4 (1.6)	2 (1.6)	1 (0.8)	4 (1.6)	6 (2.4)	4 (3.2)	2 (1.6)
Infections and infestations	2 (0.8)	1 (0.4)	1 (0.8)	0	5 (2.0)	2 (0.8)	2 (1.6)	0
COVID-19 pneumonia	2 (0.8)	1 (0.4)	1 (0.8)	0	2 (0.8)	2 (0.8)	2 (1.6)	0
Investigations	2 (0.8)	2 (0.8)	2 (1.6)	6 (4.8)	2 (0.8)	10 (4.0)	2 (1.6)	7 (5.6)
Neutrophil count decreased	0	1 (0.4)	2 (1.6)	2 (1.6)	0	5 (2.0)	2 (1.6)	3 (2.4)
White blood cell count decreased	0	1 (0.4)	0	1 (0.8)	0	2 (0.8)	0	2 (1.6)
Metabolism and nutrition disorders	3 (1.2)	2 (0.8)	1 (0.8)	0	5 (2.0)	3 (1.2)	1 (0.8)	2 (1.6)
Hypertriglyceridaemia	3 (1.2)	2 (0.8)	1 (0.8)	0	5 (2.0)	3 (1.2)	1 (0.8)	2 (1.6)

2.3.8.3. Serious adverse event/deaths/other significant events

Serious adverse event

In Study CT-P43 1.1 in healthy male subjects, there were no TESAEs in Part 1, and 4 TESAEs in Part 2 all unrelated to study drug except for one subject in the CT-P43 treatment group who experienced related grade 2 abdominal pain lower on day 7 and was hospitalised. Early appendicitis was ruled out based on CT scan result and no definite cause was identified. The subject was treated with IV antibiotics and on the next date was discharged from the hospital. The subject experienced occasional pain and diarrhoea but was recovered from the event on Day 39 (01 April 2021) and completed the study.

There were no TESAEs in Study CT-P43 1.2.

In study CT-P43 3.1, treatment period I, 8 TESAEs were reported in 8 (1.6%) patients (4 [1.6%] patients each in the CT-P43 group and EU-Stelara group). All TESAEs were considered by the investigator to be unrelated to the study drug except for COVID-19 pneumonia (1 [0.4%] patient in the CT-P43 group). All TESAEs were CTCAE Grade 3 in intensity except for one event of Grade 4 TESA of spontaneous abortion (1 [0.4%] patient in the EU-Stelara group) which was considered as not related to the study drug.

In study CT-P43 3.1, treatment period II and Follow-up Period (up to EOS), 10 TESAEs were reported in 10 (2.0%) patients (5 [2.0%], 3 [2.4%], and 2 [1.6%] patients in the CT-P43 maintenance, EU-Stelara maintenance, and Switched to CT-P43 groups, respectively).

All TESAEs were considered by the investigator to be unrelated to the study drug except for the event of tubular breast carcinoma (1 [0.4%] patient in the CT-P43 maintenance group) considered possibly related to study drug by investigator.

The majority of TESAEs were CTCAE Grade 2 or Grade 3 in intensity except for one event of Grade 5 TESA of myocardial infarction (1 [0.4%] patient in the CT-P43 maintenance group) considered not related to the study drug by the investigator.

In Treatment period II there was a TESA of pancreatitis acute in CT-P43 group which was considered unrelated to study drug by the investigator, who noted that the exact reason for the event was unknown, although the patient had grade 4 hypertriglyceridaemia (also considered unrelated to study drug) preceding the event. No action was taken with the study drug and the outcome of acute pancreatitis was recovered/resolved.

Deaths

There were no deaths reported in Study CT-P43 1.1 nor Study CT-P43 1.2.

One (0.4%) death was reported in the study CT-P43 maintenance group during the Treatment Period II; the patient died due to a TEAE of Grade 5 myocardial infarction. No patients in the CT-P43 and EU-Stelara groups during Treatment Period I and no patients in the EU-Stelara maintenance and Switched to CT-P43 groups reported TEAEs leading to death up to EOS.

This patient in CT-P43 maintenance group had a number of traditional risk factors that may have contributed to occurrence of the Grade 5 myocardial infarction, including smoking history, extreme obesity and elevated blood pressure and Grade 1 hypertriglyceridaemia and hypercholesterolaemia throughout the study. The investigator determination that the event of myocardial infarction was unrelated to the study drug. The applicant also conducted a review of all TEAEs under SOC cardiac disorders and vascular disorders within the CT-P43 clinical development programme and despite some

small imbalances in incidence of some TEAEs between groups, no clinically meaningful difference was evident.

Other significant events

Hypersensitivity reactions, injection site reactions (ISRs), infections/serious infections and malignancies were considered adverse event of special interest (AESIs).

Hypersensitivity reactions

In Study CT-P43 1.1 (Safety Set of Part 2) the number of subjects who experienced at least 1 TEAE classified as hypersensitivity reaction was reported for 2 (0.8%) subjects (1 [1.3%] subject in the CT-P43 treatment group and 1 [1.2%] subject in the EU- Stelara treatment group). The subject in the CT-P43 treatment group experienced grade 1 generalised urticaria and the subject in the EU- Stelara treatment group experienced grade 1 rash as a sign and symptom of hypersensitivity reaction. All TEAEs classified as hypersensitivity reactions were related to the study drug and grade 1 in intensity. All subjects recovered from the event without treatment. In Safety set of Part 1 there were no hypersensitivity reaction reported.

In Study CT-P43 1.2 (Safety Set) 1 subject in the EU- Stelara treatment arm (no subject in the CT-P43 and US- Stelara treatment arms) reported TEAE classified as hypersensitivity reactions, with grade 1 rash as a sign and symptom of hypersensitivity reaction. The subject recovered from the event on the same date without treatment given.

In Study CT-P43 3.1, Treatment Period I, no TEAE classified as hypersensitivity reactions was reported.

In Study CT-P43 3.1, Treatment Period II, only 1 (0.4%) patient reported a Grade 3 TEAE of hypersensitivity which was classified as a hypersensitivity reaction. The sign and symptom of the hypersensitivity was Grade 3 headache. The patient reported a hypersensitivity reaction (12 days after the Week 28 dose; the last dose for the patient) and received an oral medication (ketoprofen 100 mg) and recovered from the hypersensitivity event 39 days later; the causality of the event was assessed by the investigator as probable and no action was taken with study drug since the patient discontinued study drug before planned next dose at Week 40 dose. No TEAE classified as hypersensitivity reactions was reported in the EU-Stelara maintenance and Switched to CT-P43 groups.

Injection site reactions

In Study CT-P43 1.1 (Safety Set of Part 1), injection site reactions (ISRs) were reported for 3 (10.0%) subjects (2 [14.3%] subjects in the CT-P43 treatment group and 1 [6.3%] subject in the EU Stelara treatment group).

In Study CT-P43 1.1 (Safety Set of Part 2), the number of subjects who experienced at least 1 TEAE classified as ISR was reported for 25 (10.4%) subjects and similar between treatment groups.

The most frequently reported sign and symptom of injection site reaction was injection site erythema reported in 5 [6.3%] subjects in the CT-P43 treatment group, 6 [7.3%] subjects in the EU- Stelara treatment group, and 3 [3.8%] subjects in the US Stelara treatment group followed by injection site pain reported in 3 [3.8%] subjects in the CT-P43 treatment group, 1 [1.2%] subject in the EU-Stelara treatment group, and 3 [3.8%] subjects in the US- Stelara treatment group. All TEAEs classified as injection site reactions were related to the study drug and grade 1 or 2 in intensity. All subjects recovered from the event without treatment.

In Study CT-P43 1.2 (Safety Set) the number of subjects who experienced at least 1 TEAE classified as injection site reaction was reported for 46 (14.2%) subjects (22 [19.8%] subjects in the CT-P43 treatment arm, 14 [13.0%] subjects in the EU- Stelara treatment arm, and 10 [9.4%] subjects in the US-licensed Stelara treatment arm). Slightly higher proportion of events was reported in the CT-P43

treatment arm however, this was not considered clinically meaningful since all cases of injection site reactions were grade 1 in intensity, and all subjects quickly recovered from the event without any treatments given. The events were transient with most occurring on the day of administration and most recovering within 1-2 days.

The most frequently reported sign and symptom of injection site reaction was injection site erythema, reported in 24 (7.4%) subjects (11 [9.9%] subjects in the CT-P43 treatment arm, 11 [10.2%] subjects in the EU- Stelara treatment arm, and 2 [1.9%] subjects in the US Stelara treatment arm) followed by injection site rash reported in 14 (4.3%) subjects (6 [5.4%] subjects in the CT-P43 treatment arm, 2 [1.9%] subjects in the EU- Stelara treatment arm, and 6 [5.7%] subjects in the US- Stelara treatment arm).

In Study CT-P43 3.1, Treatment Period I, the number of patients who experienced at least 1 TEAE classified as injection site reaction was reported for 5 (1.0%) patients in total and the proportion of patients was similar between the 2 groups (3 [1.2%] and 2 [0.8%] patients in the CT-P43 and EU-Stelara groups, respectively). All TEAEs classified as injection site reactions were Grade 1 or 2 in intensity. The most frequently reported sign and symptom of injection site reactions was injection site swelling, reported in 2 (0.8%) patients each in the CT-P43 and EU-Stelara groups. All patients recovered from the event and no action was taken with study drug.

In Study CT-P43 3.1, Treatment Period II, the number of patients who experienced at least 1 TEAE classified as injection site reaction was reported for 3 (0.6%) patients (1 [0.4%] patient in the CT-P43 maintenance, none in the EU-Stelara maintenance, and 2 [1.6%] patients in the Switched to CT-P43 groups, respectively). All TEAEs classified as injection site reactions were Grade 1 or 2 in intensity.

The most frequently reported sign and symptom of injection site reactions was injection site pain, reported for 1 (0.4%) patient and 2 (1.6%) patients in the CT-P43 maintenance and switched to CT-P43 groups, respectively, and none in the EU-Stelara maintenance group. All patients recovered from the event and no action was taken with study drug.

Infections/serious infections

In Study CT-P43 1.1 (Safety Set of Part 1), TEAEs classified as infections were reported for 10 (33.3%) subjects (5 [35.7%] subjects in the CT-P43 treatment group and 5 [31.3%] subjects in the EU- Stelara treatment group). No serious infections were reported.

In Study CT-P43 1.1 (Safety Set of Part 2), the number of subjects who experienced at least 1 TEAE classified as infection was reported for 71 (29.6%) subjects and lowest in the CT-P43 treatment group (22 [27.5%] subjects in the CT-P43 treatment group, 25 [30.5%] subjects in the EU-approved Stelara treatment group, and 24 [30.8%] subjects in the US-licensed Stelara treatment group).

The most frequently reported TEAEs classified as infection included upper respiratory tract infection (12 [15.0%] subjects in the CT-P43 treatment group, 20 [24.4%] subjects in the EU-approved Stelara treatment group, and 19 [24.4%] subjects in the US-licensed Stelara treatment group), followed by gastroenteritis (4 [5.0%] subjects in the CT-P43 treatment group, 7 [8.5%] subjects in the EU-approved Stelara treatment group, and 1 [1.3%] subject in the US-licensed Stelara treatment group).

All TEAEs classified as infections were grade 1 or 2 in intensity. No serious infections were reported and most of the subjects recovered from the event.

In Study CT-P43 1.2 (Safety Set), the number of subjects who experienced at least 1 TEAE classified as infection was reported for 51 (15.7%) subjects (18 [16.2%] subjects in the CT-P43 treatment arm, 16 [14.8%] subjects in the EU-approved Stelara treatment arm, and 17 [16.0%] subjects in the US-licensed Stelara treatment arm). The most frequently reported TEAEs classified as infection included nasopharyngitis (4 [3.6%] subjects in the CT-P43 treatment arm, 8 [7.4%] subjects in the EU-

approved Stelara treatment arm, and 9 [8.5%] subjects in the US- Stelara treatment arm), followed by COVID-19 (9 [8.1%] subjects in the CT-P43 treatment arm, 5 [4.6%] subjects in the EU-approved Stelara treatment arm, and 4 [3.8%] subjects in the US Stelara treatment arm). Whilst slightly higher incidence of COVID-19 was observed in the CT-P43 treatment arm, with study period around the peak COVID-19 incidence in Japan, the opposite pattern with slightly higher incidence of nasopharyngitis in Stelara reference groups was observed and these slight numerical imbalances were not considered meaningful. All TEAEs classified as infections were grade 1 or 2 in intensity. No serious infections were reported and most of the subjects recovered from the event.

In Study CT-P43 3.1, Treatment Period I, TEAEs classified as infections were reported in 66 (13.0%) patients in total, and the proportion of patients was similar between the 2 groups (34 [13.3%] patients and 32 [12.6%] patients in the CT-P43 and EU-Stelara groups, respectively). Among them, TEAEs classified as serious infections were reported for 2 (0.8%) patients and 1 (0.4%) patient in the CT-P43 and EU-Stelara groups, respectively, and all were COVID-19 pneumonia. The TEAEs classified as infections considered by the investigator to be related to the study drug were reported for 9 (3.5%) and 8 (3.2%) patients in the CT-P43 and EU-Stelara groups, respectively.

The most frequently reported TEAE classified as infections for both groups was COVID-19 in 23 (4.5%) patients (11 [4.3%] and 12 [4.7%] patients in the CT-P43 and EU-Stelara groups, respectively). The majority of TEAEs classified as infections were Grade 1 or 2 in intensity and serious infections were Grade 3 in intensity.

In Study CT-P43 3.1, Treatment Period II, TEAEs classified as infections were reported in 86 (17.1%) patients in total, and the proportion of patients was similar among the 3 groups (39 [15.4%], 23 [18.4%], and 24 [19.4%] patients in the CT-P43 maintenance, EU-Stelara maintenance, and switched to CT-P43 groups, respectively). Among them, TEAEs classified as serious infections were reported for 1 (0.4%) patient, 2 (1.6%) patients and none in the CT-P43 maintenance, EU-Stelara maintenance, and switched to CT-P43 groups, respectively. Treatment-emergent AEs classified as serious infections were tooth abscess in 1 (0.4%) patient in CT-P43 maintenance group and COVID-19 and COVID-19 pneumonia in 1 (0.8%) patient each in EU-Stelara maintenance group. The TEAEs classified as infections considered by the investigator to be related to the study drug were reported for 7 (2.8%), 5 (4.0%), and 5 (4.0%) patients in the CT-P43 maintenance, EU-Stelara maintenance, and Switched to CT-P43 groups, respectively.

The most frequently reported TEAEs classified as infections were COVID-19 (13 [5.1%] patients in the CT-P43 maintenance group, 11 [8.8%] patients in the EU-Stelara maintenance group, and 7 [5.6%] patients in the Switched to CT-P43 group) followed by upper respiratory tract infection (10 [4.0%] patients in the CT-P43 maintenance group, 4 [3.2%] patients in the EU-Stelara maintenance group, and 7 [5.6%] patients in the Switched to CT-P43 group). The majority of TEAEs classified as infections were of Grade 1 or 2 in intensity and serious infections were of Grade 2 or 3 in intensity.

Malignancies

In studies CT-P43 1.1, CT-P43 1.2 and CT-P43 3.1 (Treatment Period I), there were no TEAEs classified as malignancy.

In Study CT-P43 3.1 (Treatment Period II), 1 (0.4%) TEAE of malignancy was reported in a postmenopausal female patient with elevated BMI. This was a Grade 3 TEAE of tubular breast carcinoma (6 days after the Week 40 dose; the last dose) classified as a malignancy after medical review. The event was recovering, and the causality of the event was assessed by the investigator as possible relatedness to study drug. The action taken with the study drug due to the event was not applicable.

2.3.8.4. Laboratory findings

Clinical laboratory

In Studies CT-P43 1.1 and 1.2, all mean clinical laboratory (clinical chemistry, haematology, and urinalysis) changes from baseline were generally small and there were no notable differences among the treatment groups in both parts.

In Study CT-P43 3.1 (Treatment Period I and II and up to EOS), there was no notable difference in the mean change from baseline in clinical chemistry, haematology, and urinalysis laboratory parameters between the 2 groups except for CRP. Since the baseline mean CRP in Treatment Period I was higher in the CT-P43 group (49.65 nmol/L and 37.99 nmol/L in the CT-P43 and EU-Stelara groups, respectively), mean decrease for CRP was also higher in the CT-P43 group throughout the visits. Mean post-baseline CRP was comparable between the 2 groups.

Table 54. Laboratory parameters of most severe CTCAE grading (Grade 3 or higher) recorded post-baseline in Study CT-P43 3.1: Safety Set/Safety-Treatment Period II Subset

	Treatment Period I (up to Week 16)		Treatment Period II and Follow-up Period (from Week 16 up to EOS)		Overall Period (up to EOS)			
CTCAE Term Grade, n (%)	CT-P43 (N=256)	EU-Stelara (N=253)	EU-Stelara Maintenance (N=125)	Switched to CT-P43 (N=124)	CT-P43 (N=256)	EU-Stelara		
						Overall (N=253)	EU-Stelara Maintenance (N=125)	Switched to CT-P43 (N=124)
Chemistry								
ALT increased								
Grade 3 (Severe)	1 (0.4)	0	0	1 (0.8)	2 (0.8)	1 (0.4)	0	1 (0.8)
Grade 4 (Life-threatening)	0	0	0	0	0	0	0	0
AST increased								
Grade 3 (Severe)	2 (0.8)	0	0	1 (0.8)	3 (1.2)	1 (0.4)	0	1 (0.8)
Grade 4 (Life-threatening)	0	0	0	0	0	0	0	0
Cholesterol high								
Grade 3 (Severe)	0	1 (0.4)	0	0	0	1 (0.4)	0	0
Grade 4 (Life-threatening)	2 (0.8)	0	0	0	2 (0.8)	0	0	0
Creatinine increased								
Grade 3 (Severe)	0	0	1 (0.8)	0	0	1 (0.4)	1 (0.8)	0
Grade 4 (Life-threatening)	0	0	0	0	0	0	0	0
GGT increased								
Grade 3 (Severe)	1 (0.4)	0	0	0	1 (0.4)	0	0	0
Grade 4 (Life-threatening)	0	0	0	0	0	0	0	0
Hyperkalemia								
Grade 3 (Severe)	1 (0.4)	0	0	0	1 (0.4)	0	0	0
Grade 4 (Life-threatening)	0	0	0	0	0	0	0	0

Hypokalemia								
Grade 3 (Severe)	0	0	0	1 (0.8)	0	1 (0.4)	0	1 (0.8)
Grade 4 (Life-threatening)	0	0	0	0	0	0	0	0
Hypertriglyceridemia								
Grade 3 (Severe)	13 (5.1)	6 (2.4)	3 (2.4)	4 (3.2)	15 (5.9)	12 (4.7)	5 (4.0)	7 (5.6)
Grade 4 (Life-threatening)	3 (1.2)	1 (0.4)	0	0	4 (1.6)	1 (0.4)	0	0
Hematology								
Lymphocyte count decreased								
Grade 3 (Severe)	1 (0.4)	0	0	0	2 (0.8)	0	0	0
Grade 4 (Life-threatening)	0	0	0	0	0	0	0	0
Neutrophil count decreased								
Grade 3 (Severe)	3 (1.2)	5 (2.0)	2 (1.6)	3 (2.4)	4 (1.6)	7 (2.8)	4 (3.2)	3 (2.4)
Grade 4 (Life-threatening)	3 (1.2)	4 (1.6)	2 (1.6)	3 (2.4)	3 (1.2)	8 (3.2)	3 (2.4)	5 (4.0)
White blood cell decreased								
Grade 3 (Severe)	1 (0.4)	1 (0.4)	2 (1.6)	1 (0.8)	1 (0.4)	4 (1.6)	2 (1.6)	2 (1.6)
Grade 4 (Life-threatening)	0	0	0	0	0	0	0	0

Vital signs, ECGs and hypersensitivity monitoring

In Study CT-P43 1.1, there were no marked differences in the hypersensitivity reaction vital sign measurements and ECGs observed after study drug administration among the treatment groups in both parts. There were no clinically notable differences in the hypersensitivity reaction vital sign measurements at any time point. Although there were some clinically notable individual low or high vital sign results no related individual vital sign measurement or ECG result was reported as a TEAE by the investigator. There were no clinically significant shifts from baseline in ECGs at 3 hours post-dose.

In Study CT-P43 1.2, mean changes from baseline in vital sign measurements were small, and there were no notable differences among the treatment groups at any time point. The majority of subjects had normal ECGs at baseline and throughout the study. One (0.9%) subject in the US-Stelara group had a normal ECG interpretation at screening but reported grade 1 ventricular extrasystoles at EOS. No treatment was given to the subject, and no other cardiac TEAEs were reported during the study.

In Study CT-P43 3.1, mean changes from baseline in vital sign and weight measurements in Treatment Period I were small, and there were no notable differences between the 2 groups at any time point. During Treatment Period II and up to EOS, mean changes from baseline were also similar, and there were no notable differences among the 3 group. The most frequently reported clinically notable vital sign results during hypersensitivity monitoring were high respiratory rate and high diastolic BP. There were no clinically significant shifts after the study drug administration compared to the results prior to study drug administration at each time point, and no apparent drug-related trends were observed in both groups. The majority of patients had normal baseline ECG results that remained normal at each time point.

Physical examination

In Studies CT-P43 1.1 and 1.2, the majority of the subjects had normal physical examination results at baseline and at any time point after drug administration. No more than 3 subjects in each treatment group shifted from normal at baseline to clinically significant abnormal for each physical examination system in both parts. There were no notable differences among the treatment groups in both parts.

In Study CT-P43 3.1, the majority of patients had normal baseline physical examination results that remained normal at each time point. There were minor shifts from baseline from normal to abnormal in Treatment Period I in a small proportion of patients with no notable differences between the 2 groups. During Treatment Period II and up to EOS, there were also minor shifts from baseline from normal to abnormal in a small proportion of patients, with no notable differences among the 3 groups.

Tuberculosis assessment

In Studies CT-P43 1.1 and 1.2, no subject was positive for the IGRA assay at Screening. No subject had any signs or symptoms present at any time point during the study that were indicative of active TB.

In Study CT-P43 3.1 (Treatment Period I), most patients had negative IGRA results at baseline with 55 (10.8%) patients having positive IGRA results at baseline, who were enrolled after 3-week TB prophylaxis prior to the first administration of the study drug according to the exclusion criterion #9. There were no patients who showed signs or symptoms of TB during Treatment Period I.

In Study CT-P43 3.1 (Treatment Period II), a total of 17 TEAEs were reported as 15 cases of latent TB, 1 case of tuberculosis, and 1 case of IGRA positive result based on IGRA test results at Week 16. 15 (3.0%) patients (7 [2.8%] patients in the CT-P43 maintenance group, 4 [3.2%] patients in the EU-Stelara maintenance group, and 4 [3.2%] patients in the Switched to CT-P43 group) were reported TEAEs of latent TB (defined as a positive result of IGRA with negative examination of chest X-ray) during the study period; this included 12 patients (4 patients each in the CT-P43 maintenance group, EU-Stelara maintenance group and Switched to CT-P43 group) who showed positive IGRA conversions, and 3 patients in the CT-P43 maintenance group who had initially positive IGRA results at Week 16 and negative IGRA results after IGRA retest. One patient (0.8%) in the EU-Stelara maintenance group reported a TEAE of tuberculosis (reported term: respiratory tuberculosis, not confirmed bacteriologically, molecularly or histologically), but active TB was ruled out based on the negative results of sputum and TB culture test. One patient (0.8%) in the Switched to CT-P43 group reported a TEAE of IGRA positive result, and follow-up IGRA result at Week 28 unscheduled visit was negative. All of 17 patients started proper TB prophylaxis and did not complain of any signs or symptoms of TB during study period. Throughout the study, patients were monitored for the clinical signs and symptoms of TB and no active TB was reported, and no patients complained of signs or symptoms of TB during study period. Overall, the results of tuberculosis assessment were comparable among the 3 groups.

2.3.8.5. *In vitro* biomarker test for patient selection for safety

Not applicable

2.3.8.6. *Safety in special populations*

Not applicable.

2.3.8.7. *Immunological events*

Study CT-P43 1.1

In the Safety Set of Part 1, 3 (10.0%) subjects (1 [7.1%] subject in the CT-P43 treatment group and 2 [12.5%] subjects in the EU- Stelara treatment group) had a positive ADA test result at baseline prior to study drug administration. NAb results were all negative for these subjects. The number of subjects who had positive ADA results throughout the study were similar between the 2 treatment groups with an increasing trend throughout the study. At EOS visit, 7 (23.3%) subjects (4 [28.6%] subjects in the CT-P43 treatment group and 3 [18.8%] subjects in the EU- Stelara treatment group) had a positive ADA test result. The proportion of subjects who had at least 1 post-treatment ADA positive result was comparable, 6 [42.9%] subjects in the CT-P43 treatment group and 6 [37.5%] subjects in the EU-

Stelara treatment group). Only 1 (6.3%) subject in the EU- Stelara treatment group had NAb positive result at Day 85 and EOS visit.

In the Safety Set of Part 2, 8 (3.3%) subjects (2 [2.5%] subjects in the CT-P43 treatment group, 2 [2.4%] subjects in the EU- Stelara treatment group, and 4 [5.1%] subjects in the US- Stelara treatment group) had a positive ADA test result at baseline prior to study drug administration. However, there was no pre-dose NAb positive result in Part 2. The number of subjects who had positive ADA results showed an increasing trend throughout the study in the order of US- Stelara treatment group, EU- Stelara treatment group and CT-P43 treatment group. At EOS visit, 57 (23.8%) subjects (13 [16.3%] subjects in the CT-P43 treatment group, 19 [23.2%] subjects in the EU-approved Stelara treatment group, and 25 [32.1%] subjects in the US- Stelara treatment group) had a positive ADA test result. The number of subjects who had at least 1 post-treatment ADA positive result was also lowest in the CT-P43 treatment group, (13 [16.3%] in the CT-P43 treatment group, 24 [29.3%] in the EU- Stelara treatment group, and 34 [43.6%] subjects in the US- Stelara treatment group). At EOS visit, 17 (7.1%) subjects (4 [5.0%] subjects in the CT-P43 treatment group, 4 [4.9%] subjects in the EU-approved Stelara treatment group, and 9 [11.5%] subjects in the US-licensed Stelara treatment group) showed positive NAb results. The number of subjects who had at least 1 post-treatment NAb positive result was 20 (8.3%) subjects (5 [6.3%] subjects in the CT-P43 treatment group, 6 [7.3%] subjects in the EU-approved Stelara treatment group, and 9 [11.5%] subjects in the US-licensed Stelara treatment group).

The proportions of subjects who had at least 1 post-treatment ADA positive result and NAb positive result showed that CT-P43 appeared to be less immunogenic with lower number of subjects with positive ADA results compared to EU or US Stelara. No anaphylaxis or serious hypersensitivity reactions were reported among any of the 3 treatment groups. Hypersensitivity reactions and injection site reactions were not frequent and the proportion was comparable. There were no significant differences seen in immunogenic safety events among the 3 treatment groups.

Median ADA titres were generally comparable among 3 treatment groups. Mean ADA titres showed slight fluctuation throughout the study period, however, should be viewed with caution due to the small number of subjects. Eight subjects (2, 2 and 4 subjects in the CT-P43, EU-Stelara and US-Stelara treatment groups, respectively) had significantly high ADA titre (≥ 2430). For the 2 subjects in CT-P43 group with high ADA Titre (≥ 2430) in Study CT-P43 1.1 Part 2, one had an unrelated Grade 1 TEAE of oropharyngeal pain and the other did not have any TEAE. Similarly, for the Stelara groups no related or serious TEAEs were associated with higher ADA titres. There was no significant impact on the safety results by high ADA titre, while high ADA titre did seem to be associated with reduced serum concentrations.

In Study CT-P43 1.1 Part 2, the overall AE incidence was generally similar between the Safety Set – ADA Negative Subset and Safety Set – ADA Positive Subset and was also comparable among 3 treatment groups.

Study CT-P43 1.2

In the Safety Set, 4 (3.6%) subjects in the CT-P43 treatment arm had a positive ADA test result at baseline prior to study drug administration. However, NAb results were all negative for these subjects. The number of subjects who had positive ADA results showed slightly higher in the order of EU- Stelara treatment arm, US- Stelara treatment arm and CT-P43 treatment arm, and also with an increasing trend throughout the study. At EOS visit, 90 (27.7%) subjects (18 [16.2%] subjects in the CT-P43 treatment arm, 38 [35.2%] subjects in the EU approved Stelara treatment arm, and 34 [32.1%] subjects in the US-licensed Stelara treatment arm) had a positive ADA test result. The number of subjects who had at least 1 post-treatment ADA positive result lowest in the CT-P43 treatment arm,

(18 [16.2%] in the CT-P43 treatment arm, 48 [44.4%] in the EU- Stelara treatment arm, and 42 [39.6%] subjects in the US- Stelara treatment arm).

There was no pre-dose NAb positive result. At EOS visit, 44 (13.5%) subjects (14 [12.6%] subjects in the CT-P43 treatment arm, 15 [13.9%] subjects in the EU-approved Stelara treatment arm, and 15 [14.2%] subjects in the US-licensed Stelara treatment arm) showed positive NAb results. The number of subjects who had at least 1 post-treatment NAb positive result was 48 (14.8%) subjects (14 [12.6%] subjects in the CT-P43 treatment arm, 18 [16.7%] subjects in the EU-approved Stelara treatment arm, and 16 [15.1%] subjects in the US-licensed Stelara treatment arm). The proportions of subjects who had at least 1 post-treatment ADA positive result showed that CT-P43 appeared to be less immunogenic. However, NAb positive results although still slightly lower with CT-P43, were generally more similar. No anaphylaxis or serious hypersensitivity reactions were reported and there were no significant differences seen in immunogenic safety events among the 3 treatment arms.

Mean and median ADA titres showed slight fluctuation throughout the study period, however, should be viewed with caution due to the small number of subjects.

A total of 31 subjects (9, 10 and 12 subjects in the CT-P43, EU-Stelara and US-Stelara treatment groups, respectively) had significantly high ADA titre (≥ 2430). There was no significant impact on the safety results by high ADA titre while high ADA titre did seem to be associated with reduced serum concentrations.

Study CT-P43 3.1

The immunogenicity results in Study CT-P43 3.1 showed that CT-P43 appeared to be less immunogenic compared to EU Stelara, where 33 (12.9%) patients and 86 (34.0%) patients in the CT-P43 and the EU Stelara treatment groups, respectively, were found to have at least 1 ADA positive result after study drug exposure up to EOS.

The baseline, demographic and disease characteristics which might have possibly impacted the immunogenicity were generally similar between the 2 treatment groups. In addition, the applicant did not identify any other factors including assay methodology, sample handling and the timing of sample collection which could have impacted the immunogenicity. As discussed for Study CT-P43 1.1 above, the applicant considered that these differences may be attributed to the use of different cell lines in manufacturing CT-P43 and EU-Stelara.

The single transition from EU-Stelara to CT-P43 at Week 16 was not observed to have an impact on immunogenicity: the number of patients who showed at least one ADA positive result obtained from Week 16 post-dose up to EOS were 27 (21.6%) patients and 25 (20.2%) patients in the EU-Stelara maintenance and the Switched to CT-P43 treatment groups, respectively. Of the patients who had all ADA negative results before single transition at Week 16, a similarly small number of patients reported at least 1 ADA (or NAb) positive result in Treatment Period II in both treatment groups (6.8% [6.4%] and 4.7% [2.9%] for the EU-Stelara maintenance and the Switched to CT-P43 treatment groups, respectively).

The median ADA titre results up to EOS were generally similar between the patients who received CT-P43 and the patients who received EU-Stelara or were switched to receive CT-P43.

While mean ADA titres were higher in the CT-P43 and CT-P43 maintenance treatment groups than the other treatment groups, the applicant considered this might have been derived by 2 patients who showed significantly high ADA titres (≥ 21870) from Week 12. One patient showed ADA positive and NAb positive from Week 4 and the other patient from Week 12.

All patients with significantly high ADA titre (≥ 21870) did not report any AEs related to immune response including ISR and hypersensitivity. In the small number of observed cases, there were no

convincing signs that high ADA titre resulted in reduced efficacy, although the limited dataset is acknowledged.

Impact of ADA on Safety

There was no apparent correlation between the presence of ADA and the occurrence of TEAE, TESAE, ISR or hypersensitivity reactions.

In Study CT-P43 3.1 there were 2 ISRs in the ADA positive subgroup of CT-P43 treatment group and 1 ISR in the ADA positive subgroup of EU-Stelara treatment group. Due to a relatively small number of patients in ADA positive subgroups, the comparative safety data should be interpreted with caution. Further investigations on the two patients with ISR in the ADA positive subgroup of CT-P43 treatment group were conducted and it was confirmed that both TEAEs occurred in Treatment Period I, were grade 1 in intensity, non-serious and recovered. These patients' sign and symptom were injection site swelling and injection site erythema/pruritus/swelling, respectively. The one patient with ISR in the ADA positive subgroup of EU-Stelara treatment group reported a grade 1 non-serious TEAE, also in Treatment Period IA, of injection site erythema and swelling that also recovered without treatment.

One patient in the ADA positive subgroup of the CT-P43 treatment group experienced hypersensitivity reaction. The event occurred in Treatment Period II and was grade 3 non-serious, related TEAE of headache. The patient received oral medication of ketoprofen and recovered. Of note the patient had several concurrent medical conditions and was on a number of medications that have also been associated with headache and is discussed further within the safety section. Otherwise, there were no other hypersensitivity related TEAEs occurring in ADA positive subjects in CT-P43 group in Study CT-P43 3.1.

Table 55. Proportion of Patients with TEAE, TESAE, TEAE Classified as Injection Site Reactions and Hypersensitivity Reactions by Posttreatment ADA Status in Study CT-P43 3.1 (Safety Set)

Number of Patients (%) with at Least 1 Adverse Event	Overall Period (up to EOS)			
	CT-P43 (N=256)		EU-Stelara (N=253)	
ADA Status	ADA Positive (N=33)	ADA Negative (N=223)	ADA Positive (N=86)	ADA Negative (N=165)
TEAE	19 (57.6%)	118 (52.9%)	45 (52.3%)	94 (57.0%)
TESAE	0	9 (4.0%)	2 (2.3%)	6 (3.6%)
Injection Site Reactions	2 (6.1%)	2 (0.9%)	1 (1.2%)	3 (1.8%)
Hypersensitivity Reactions	1 (3.0%)	0	0	0

Source: [REDACTED]

Note: Percentages are calculated by using the number of patients in each ADA subgroup as denominator.

2.3.8.8. Safety related to drug-drug interactions and other interactions

Not applicable.

2.3.8.9. Discontinuation due to adverse events

In Studies CT-P43 1.1, CT-P43 1.2 and CT-P43 3.1 (Treatment Period I) there were no TEAEs leading to study discontinuation.

In Study CT-P43 3.1 (Treatment period II and FU period), 7 (1.4%) patients experienced at least 1 TEAE leading to study drug discontinuation (5 [2.0%] patients in the CT-P43 maintenance group, 1 [0.8%] patient each in the EU-Stelara maintenance and switched to CT-P43 groups). The TEAEs leading to study drug discontinuation were headache, hepatitis B, hepatitis B DNA assay positive, hepatitis B surface antigen positive, myocardial infarction, prostatic mass, and respiratory failure. Only the TEAEs of Grade 3 headache and Grade 2 hepatitis B DNA assay positive were considered related to study drug by the investigator, which led to study drug discontinuation. The Grade 3 TEAE of headache was discussed above. The Grade 2 hepatitis B DNA assay positive occurred in the EU-Stelara group and was considered possibly related.

2.3.8.10. Post marketing experience

Not applicable.

2.3.9. Discussion on clinical safety

Safety data on CT-P43 is available from three completed clinical studies, two Phase I studies, and one Phase III study, in which safety was assessed as part of the secondary study objectives.

In the present MAA, only the 45 mg/0.5 mL and 90 mg/1.0 mL prefilled syringe (PFS) presentations and IV 130mg vial pf CT-P43 are applied for. The applicant discussed that the potential for medication errors due to the absence of 45 mg SC vial at present is low, given the differences of devices (PFS vs SC vial) in multiple aspects including appearance, functions, populations to be prescribed, posology and method of administration which are clearly indicated in SmPC and Package Leaflet. It is considered that the risk can be mitigated through the product information outlining the need for use of other ustekinumab products for paediatric plaque psoriasis patients weighing less than 60 kg. As such the product information was updated to highlight there is no dose form that allows weight-based dosing for paediatric patients below 60 kg and that patients weighing less than 60 kg should be accurately dosed on a mg/kg basis using another ustekinumab product for which a 45 mg solution for injection in vial presentation enabling weight-based dosing, is available. This is acceptable.

Patient exposure

In the clinical study programme of CT-P43, the Safety Set includes data from 1104 subjects in the 3 clinical studies and specifically for CT-P43, safety data is available from 380 patients with moderate to severe plaque psoriasis and 205 healthy male subjects.

In studies CT-P43 1.1 and 1.2, healthy male subjects received a single dose of CT-P43 (45mg SC injection via PFS). In study CT-P43 3.1, a total of 5 doses of study drug CT-P43 or EU-Stelara were to be administered. Patients with moderate to severe plaque psoriasis were to receive either 45 or 90 mg of CT-P43 or Stelara by SC injection via PFS Weeks 0, 4, 16, 28, and 40 based on patient's baseline/week 16 body weight.

Study CT-P43 1.1

For Study CT-P43 1.1, a total of 270 healthy male subjects were enrolled. Part 1 was a pilot study designed to collect initial preliminary safety data from 30 subjects before initiation of Part 2. Of the 241 subjects randomised in Part 2, 11 (4.6%) discontinued the study, with similar numbers between the three groups. Demographics and baseline characteristics were generally similar between treatment groups.

Study CT-P43 1.2

In Study CT-P43 1.2, 331 subjects were randomly assigned to a treatment arm (114 subjects in the CT-P43 treatment arm, 110 subjects in the EU-approved Stelara treatment arm, and 107 subjects in the US-licensed Stelara treatment arm). There was a similar number of subject discontinuations between the three groups, 5, 5, and 4 subjects. All subjects enrolled were Japanese with mean age of 34.8 years and generally similar demographic and baseline characteristics.

Study CT-P43 3.1

In Study CT-P43 3.1, a total of 509 patients with moderate to severe PsA were enrolled and randomly assigned to one of the 2 treatment groups in a 1:1 ratio (256 and 253 patients in CT-P43 and Stelara treatment groups, respectively). Prior to dosing at Week 16, all patients in the Stelara group were randomly assigned again in a ratio of 1:1 to either continue Stelara maintenance or undergo a Switch to CT-P43. Of the 253 subjects initially randomised to the EU Stelara group, 124 were switched to CT-P43 maintenance from Week 16 to 40, whilst 125 subjects remained in the EU-Stelara maintenance group. The EMA Guidelines, Guideline on Immunogenicity assessment of therapeutic proteins EMEA/CHMP/BMWP/42832/2005 Rev1 and Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues - Revision 1 EMEA/CHMP/BMWP/42832/2005 Rev1, state that *'In case of continuous chronic treatment, immunogenicity data for one year of treatment should normally be available pre-authorisation but shorter follow up is possible with a proper justification'* and in relation to Clinical Safety that *'Comparative safety data should normally be collected pre-authorisation, their amount depending on the type and severity of safety issues known for the reference product. The duration of safety follow-up pre-authorisation should be justified'*. The applicant has provided sufficient justification for the treatment duration of 40 weeks, with additional 12 weeks of follow up, to give a 52-week total duration, based on the available data from Stelara, its characterised safety profile and relatively low immunogenicity.

There were generally balanced numbers of subjects who received the 45mg SC or 90mg SC dose across the treatment groups, with approximately 75% overall receiving the 45mg SC dose. There were no differences in demographic or baseline characteristics considered to impact on similarity assessment. For all scheduled doses up to Week 40, the proportions of patients who had total 5 doses administered were similar among the treatment groups (243 [94.9%] patients in the CT-P43 group and 242 [95.7%] patients in the EU-Stelara group).

Adverse events

Study CT-P43 1.1

Based on the summary of adverse events, no major differences between CT-P43 and EU and US Stelara were observed. For Part 2, the total number of TEAEs were 212 in CT-P43, 224 in EU Stelara and 159 in US Stelara respectively. There were no TEAEs leading to death nor to study discontinuation and there were no TEAEs of malignancy nor serious infection. There were no evident differences in the number of subjects with TEAEs classified as hypersensitivity reaction, injection site reactions or infections between the three groups. Whilst there were slight imbalances in the number of subjects with some PT TEAEs in the CT-P43 treatment group compared to EU and US Stelara groups, overall, the numbers were low and no specific trends were evident. In addition, most of the TEAEs were Grade 1 or 2 in intensity. In CT-P43 treatment group there was only 1 Grade 3 TEAE, and this was considered unrelated to study treatment.

Study CT-P43 1.2

The total number of TEAEs were generally balanced between the three groups, 87, 94 and 79 in CT-P43, EU and US Stelara respectively. There was a slight increase in the number of subjects with at least 1 TEAE in CT-P43 group (61) compared to the EU (54) and US Stelara (48) groups, as well as

slightly higher number of subjects with at least 1 related TEAE in the CT-P43 group. Overall, these numerical differences were considered low.

There was a higher total number of TEAEs classified as injection site reactions in 22 subjects in the CT-P43 group, compared to the EU and US Stelara groups, 14 and 10 subjects respectively, which were all considered related to the study drug. The applicant discussed the slight imbalance in ISRs observed for CT-P43 in Study CT-P43 1.2. Following review of product related factors including quality attributes, as well as injection related factors and an exploratory review of patient related factors including age, BMI and atopy history no evident differences were observed to explain the imbalance in occurrence of ISRs observed in this study. The applicant highlighted also that although a numerical imbalance was observed, all these ISRs were grade 1 in intensity, predominantly mild injection site erythema and all subjects recovered quickly without any treatments given. Thus the slight imbalance was not considered clinically meaningful and in the other two studies, CT-P43 1.1 Part 2 and CT-P43 3.1, the incidences of ISR were comparable between CT-P43 and EU-Stelara. This is agreed.

All TEAEs considered related in Study CT-P43 1.2 for all three treatment groups were Grade 1 or 2 in intensity. In terms of unrelated TEAEs, 12 Grade 3 and 4 TEAEs were reported, all in the SOC Investigations; and these were all events of blood CPK increased, and blood triglycerides increased. Numbers were similar between the three groups and all of these TEAEs were considered unrelated to the study drug.

Study CT-P43 3.1

In Treatment Period I, there was a higher occurrence of patients with ≥ 1 TEAE in the CT-P43 group 95 (37.1%) compared to EU-Stelara 75 (29.6%). Of these, the number (%) of patients with ≥ 1 Related TEAE and the total number of TEAEs in the CT-P43 group in Treatment period I were also slightly higher, 158 in the CT-P43 group compared to the EU-Stelara group, 110. The applicant was requested to discuss the higher frequency of TEAEs, and of patients with ≥ 1 TEAE, including related TEAEs, in the CT-P43 group compared to EU Stelara. The only PT where the difference in the incidence between the treatment groups was 2 or more % higher in the CT-P43 group compared to EU Stelara was hypertension 7 vs 1, see below. On review of the remaining TEAEs, their grade (mostly grade 1 and 2) and relatedness to the study drug (mostly unrelated), this did not raise any concern for a specific pattern or trend that would question the similarity in terms of safety for CT-P43 compared to EU Stelara.

In Treatment Period II, whilst the number of patients with at least 1 TEAE was similar between the two arms EU-Stelara and Switch to CT-P43, 51 vs 52, the actual total number of TEAEs was higher for the Switch to CT-P43 group compared to EU Stelara 100 vs 83. There was also a slightly higher number (%) of patients with ≥ 1 Related TEAE in the Switch to CT-P43 group (8 [6.4%] in the EU-Stelara maintenance group and 12 [9.7%] in the Switched to CT-P43 group) in Treatment Period II. It is acknowledged the overall numbers of related TEAEs were low, the transition of subjects from treatment with EU-Stelara to CT-P43 is not a recommendation in the EMA guidelines and thus any potential imbalances in safety data between the patients who remained in the EU Stelara arm after the switch and the patients Switched to CT-P43 treatment was requested to be discussed. On review of the specific PTs, only minor imbalances were noted and the applicant highlighted that there was one subject in the Switch to CT-P43 treatment group who reported 12 TEAEs, all deemed unrelated to study drug except for one TEAE of pneumonia viral. The applicant highlighted that if this subject who reported a total of 12 TEAEs in Treatment Period II and Follow-up was excluded from the Switch to CT-P43 treatment group, the total numbers of TEAEs between the EU Stelara and Switch to CT-P43 treatment groups would be comparable, which is acknowledged. On review of the related TEAEs, the imbalance was very minor and the only PT in which a higher than 2% difference between groups was observed was ALT increase (0 in EU Stelara maintenance vs 4 in Switch to CT-P43 group). The small

numerical difference in the TEAE of ALT increase is not considered to indicate any discernible differences in safety profile for CT-P43 compared to EU Stelara and the applicant conclusion that switching from EU-Stelara to CT-P43 does not show any new safety signals is agreed.

No major difference was observed in Number (%) of patients with ≥ 1 TESAEs nor TEAEs leading to discontinuation of study drug between the Stelara maintenance and Switch to CT-P43 group.

In Treatment period I, the most common TEAEs occurring in $\geq 3\%$ subjects were COVID-19 and upper respiratory tract infection and in Treatment period II, the most common TEAEs occurring in at least 3% were COVID-19. During Treatment Period II, 3 TEAEs of positive results for HBV tests were reported, 1 in EU Stelara maintenance and 2 in the CT-P43 maintenance group. For the 2 subjects on CT-P43 maintenance there were new positive HBsAg and HBV DNA test results respectively. Both cases were Grade 2, and the investigator considered both to be unrelated to study drug. For the patient in the EU-Stelara maintenance group) the event was reported as a TEAE of hepatitis B DNA assay positive, considered study drug related by the investigator. In all 3 cases the study drug was withdrawn.

On review of the TEAEs in Study CT-P43 3.1, a slightly higher occurrence of patients who experienced at least 1 TEAE in SOC Gastrointestinal disorders for CT-P43 compared to EU Stelara in both Treatment period I and II was noted. However, most TEAEs occurred only once and were considered unrelated to study drug and no pattern or trend suggestive of a different safety profile specifically related to TEAEs in SOC gastrointestinal disorders was evident.

For the PT Headache, on review of the three studies, a slightly higher occurrence of headache in the CT-P43 treatment group compared to EU/US Stelara was noted. The overall incidence was still low however and was within the expected frequency of headache as per the SmPC for Stelara. On review of the specific TEAEs of headache, no obvious pattern in the occurrence of headaches was observed that would preclude a conclusion on similarity in terms of safety for CT-P43 and Stelara.

In Study CT-P43 3.1 there was an imbalance in the number of subjects with TEAEs of hypertension in the CT-P43 group compared to EU-Stelara in Treatment Period I, numerical imbalance in reported TEAEs of hypertension were observed in Study CT-P43 3.1 Treatment Period I (7 [2.7%] and 1 [0.4%] patients, respectively). On review, a number of subjects had background history of hypertension, all but one TEAE were deemed unrelated to study drug and no serious events occurred. This pattern was not observed in Treatment Period II or Studies CT-P43 1.1 or 1.2 and thus the slight imbalance observed was not considered clinically meaningful nor relevant in terms of similarity assessment

Throughout the study period, the proportions of patients who experienced at least 1 TEAE considered to be related to the study drug were similar between the treatment groups.

In both Treatment Period I and II, the majority of TEAEs reported were considered CTCAE Grade 1 or 2 in intensity. Overall, 39 (7.7%) patients experienced at least 1 Grade 3 TEAE, and 9 (1.8%) patients experienced at least 1 Grade 4 TEAE with comparable results between the groups.

For Grade 3, the most frequently reported TEAEs were hypertriglyceridaemia and for Grade 4, the most frequently reported TEAEs were neutropenia. Except for 1 TEAE of myocardial infarction in 1 (0.4%) patient in the CT-P43 maintenance group, no Grade 5 TEAEs were reported in any group.

The adverse drug reactions are adequately listed in section 4.8 of the SmPC and are in line with the ones of the reference medicinal product.

Serious adverse events and deaths, other significant events

The occurrence of TESAEs related to the study drug was relatively low in the 3 studies (one in study CT-P43 1.1, none in study CT-P43 1.2 and one in study CT-P43 3.1). In study CT-P43 1.1, the TESA was a grade 2 event of abdominal pain in the CT-P43 group, considered serious due to hospitalisation.

However, the subject was discharged the next day, and the AE was resolved at the end of study. In study CT-P43 3.1 (Treatment Period I) in CT-P43 group of COVID-19 pneumonia one event was considered related to study treatment, with seriousness criteria met for initial hospitalisation. The event resolved and study drug was continued.

No deaths were reported in studies CT-P43 1.1 or 1.2. One death was reported in study CT-P43 3.1 maintenance group (a Grade 5 TEAE of myocardial infarction). The investigator considered this event to be unrelated to the study drug. On review of other TEAEs in the SOC cardiac and vascular disorders within the CT-P43 clinical development programme, no clinically relevant differences were observed. Thus this single unrelated Grade 5 TEAE was not considered to impact upon the similarity assessment for CT-P43 and Stelara. The Stelara SmPC contains a warning for cardiovascular events as events of myocardial infarction and cerebrovascular event have been observed in the post-marketing setting.

Adverse event of special interest (AESIs) were hypersensitivity reactions, injection site reactions, infections/serious infections and malignancies. Appropriate information for the AESIs is provided in the product information.

Laboratory abnormalities

Study CT-P43 1.1 and 1.2

No significant findings that would impact similarity assessment were reported in terms of laboratory results, vital signs, physical examination, ECGs or TB assessments and any differences observed were considered in line with expected variability.

Study CT-P43 3.1

For clinical chemistry, the most frequently reported grade 3 or higher clinical chemistry parameter was hypertriglyceridaemia. The applicant provided a summary of all events of blood triglyceride increase/hypertriglyceridaemia that occurred in CT-P43 clinical development programme summarising their intensity, relatedness and any associated TEAEs. In general, the occurrence of hypertriglyceridaemia/increased triglycerides was comparable between treatment arms in Study CT-P43 1.1, 1.2 and Treatment Period I of CT-P43 3.1. In Treatment Period II and the Follow-up Period of Study CT-P43 3.1, the TEAEs of blood triglyceride increased or hypertriglyceridaemia were slightly more frequently reported in the CT-P43 maintenance and Switched to CT-P43 group compared to the EU-Stelara maintenance group (6 [2.4%] patients in the CT-P43 maintenance group, 2 [1.6%] patients in the EU-Stelara maintenance group and 5 [4.0%] patients in Switched to CT-P43 group). All the events were considered by the investigator to be unrelated to the study drug, except for one patient in Switch to CT-P43 group. The related case occurred in a male subject with increased BMI and abnormal triglyceride level at screening, who had two TEAEs of Grade 2 hypertriglyceridaemia during the study period, the first considered related and the second considered unrelated, both of which recovered/resolved. The relatively small difference in occurrence of TEAEs of hypertriglyceridaemia or increased triglyceride levels observed in Study CT-P43 3.1, Treatment Period II to EOS, most of which were considered unrelated to study drug, does not preclude a conclusion on similarity in terms of safety. In Study CT-P43 3.1, one subject in CT-P43 group had a TEAE of pancreatitis acute considered unrelated to study drug in association with Grade 4 hypertriglyceridaemia. This patient however had a significantly elevated triglyceride level at screening (11.44 mmol/L) preceding study drug administration.

For the other laboratory values, vital sign measurements, ECG finding, hypersensitivity monitoring and TB assessments, there were no significant findings that were considered to impact on similarity assessment.

Discontinuation due to adverse events

There were no TEAEs leading to study discontinuation in Studies CT-P43 1.1, 1.2 or 3.1 (treatment period I).

In study CT-P43 (treatment period II), a slightly higher number of patients experiencing at least 1 TEAE leading to study drug discontinuation was observed in the CT-P43 maintenance group 5 (2.0%) compared to the Stelara maintenance 1 (0.8%) and Switch to CT-P43 group 1 (0.8%), respectively. Of these 5 of 7 TEAEs were considered unrelated to study drug. The only TEAEs considered related that led to study drug discontinuation was a Grade 3 TEAE of headache for the CT-P43 maintenance group, and a Grade 2 event of Hepatitis B DNA assay positive for the EU-Stelara group. Another patient in the CT-P43 maintenance group also had a TEAE of Hepatitis B surface antigen positive leading to drug discontinuation, but this was not considered related to study drug. Overall, the numbers are low, and no trend in reason for discontinuing is evident to draw any conclusion.

Immunological events

In both healthy subjects and plaque psoriasis patients, the ADA and NAb incidences were lower in the CT-P43 treatment group compared to the EU-/US-Stelara treatment groups.

Study CT-P43 1.1

In Study CT-P43 1.1 Part 2, the proportions of healthy male subjects who had at least 1 post-treatment ADA positive result and NAb positive result showed that CT-P43 appeared to be less immunogenic than the reference products, EU and US Stelara.

Median ADA titres were similar between three treatment groups. Mean ADA titres showed slight fluctuation throughout the study period, for the three treatment groups, however on reviewing the 8 subjects with highest ADA titres (≥ 2430) there were no related or serious TEAEs for any subjects.

For both the ADA positive and negative subsets, the number of subjects with hypersensitivity and injection site reactions were low overall and slight imbalance observed was not considered clinically meaningful.

Study CT-P43 1.2

Similar to Study CT-P43 1.1, the proportions of subjects in Study CT-P43 1.2 who had at least 1 post-treatment ADA positive result showed that CT-P43 appeared to be less immunogenic than reference EU and US Stelara. For both studies in healthy male subjects, the applicant considers that as the baseline demographic characteristics were similar between groups, that the observed difference in immunogenicity could be attributed to the use of different cell lines in manufacturing CT-P43 and Stelara. The applicant's rationale is followed by the CHMP.

Whilst slight fluctuations in mean and median ADA titres were observed throughout the study, with higher mean titres at EOS visit in the CT-P43 treatment group, these differences did not appear clinically meaningful. On reviewing the 31 subjects overall with significantly high ADA titres ≥ 2430 , numbers were similar amongst the three groups. There were no related nor serious TEAEs reported after the high ADA titre for any subject with a high ADA titre ≥ 2430 . For almost all of these subjects the serum concentration ($\mu\text{g/mL}$) was below the limit of quantification.

Study CT-P43 3.1

Similar to the Phase I studies in healthy male subjects, the immunogenicity results in Study CT-P43 3.1 show that CT-P43 appeared to be less immunogenic where 33 (12.9%) patients and 86 (34.0%) patients in the CT-P43 and the EU Stelara treatment groups, respectively, were found to have at least 1 ADA positive results after study drug exposure up to EOS.

In terms of transition from EU-Stelara to CT-P43 at Week 16, no evident impact on immunogenicity was observed, on review of the data on positive conversion in ADA or NAb, which for both were lower in the Switch to CT-P43 group.

Similar to the Phase I studies, the median ADA titres were comparable between the study groups.

However, the mean titres were higher for the CT-P43 group in Treatment period I and for the CT-P43 maintenance group also in Treatment Period II to EOS. The applicant considered this may have been due to 2 patients who showed significantly high ADA titres (≥ 21870) from Week 12. Regardless for the 6 subjects with significantly high ADA titre ≥ 21870 no related nor serious TEAEs were reported after the high ADA titre. The serum concentration was below the limit of quantification for all six subjects, however the high ADA titres did not appear to show any evident trend for reduced efficacy based on the percent improvement from baseline for PASI scores. Overall, there was no apparent correlation between the presence of ADA and the occurrence of TEAE, TESA, ISR or hypersensitivity reactions.

The list of safety concerns in the risk management plan (RMP) are in line with the one of the reference medicinal product (see section 2.7.) .

2.3.10. Conclusions on the clinical safety

Overall, the CT-P43 clinical development programme and design of the studies is adequate to evaluate the comparability of CT-P43 and its reference product EU-Stelara, in terms of safety and immunogenicity. Whilst some numerical differences were observed in occurrence of total number of TEAEs between the CT-P43 and Stelara treatment groups, and within some specific PTs, these differences were small and were not considered clinically meaningful.

Overall, no major differences in safety profile between CT-P43 and EU-Stelara have been identified based on the available data and the two products are concluded to be biosimilar in terms of clinical safety. In terms of immunogenicity, subjects (both healthy volunteers and patients) treated with CT-P43 had lower ADA and nAb frequencies than subjects treated with Stelara. No immunogenicity related difference was observed in the safety profile of the two products.

2.4. Risk Management Plan

2.4.1. Safety concerns

Table 56. Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Serious infections (including mycobacterial and salmonella infections) • Malignancy • Cardiovascular events • Serious depression including suicidality • Venous thromboembolism

Summary of safety concerns	
	Exposure during pregnancy
Missing information	- Long-term safety in paediatric psoriasis patients 6 years and older - Long-term impact on growth and development in paediatric psoriasis patients 6 years and older - Long-term safety in adult patients with moderately to severely active Crohn's disease

2.4.2. Pharmacovigilance plan

Table 57. Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestone	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
None				

2.4.3. Risk minimisation measures

Table 58. Summary of risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious infections (including mycobacterial and salmonella infections) (Important potential risk)	<u>Routine risk minimisation measures:</u> - SmPC Sections 4.3, 4.5, 4.6 and 4.8 - SmPC Section 4.4 where guidance and management of serious infections are included. - PL Sections- 2 and 4 <u>Legal status:</u> Prescription only medicine Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication. <u>Additional risk minimisation measures:</u> None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> Adverse reaction follow-up Questionnaire <u>Additional pharmacovigilance activities:</u> None
Malignancy (Important potential risk)	<u>Routine risk minimisation measures:</u> - SmPC Section 4.8 - Guidance is given for the prescribers in SmPC Section 4.4, the patients greater than 60 years of age, patients with medical history of prolonged immunosuppressant therapy or PUVA treatment should be monitored for NMSC. - PL Section- 2 <u>Legal status:</u> Prescription only medicine Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication. <u>Additional risk minimisation measures:</u> None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> Adverse reaction follow-up Questionnaire <u>Additional pharmacovigilance activities:</u> None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cardiovascular Events (Important potential risk)	<u>Routine risk minimisation measures:</u> None <u>Legal status:</u> <i>Prescription only medicine</i> <i>Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.</i> <u>Additional risk minimisation measures:</u> None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> Adverse reaction follow-up Questionnaire <u>Additional pharmacovigilance activities:</u> None
Serious depression including suicidality (Important potential risk)	<u>Routine risk minimisation measures:</u> • <i>SmPC Section 4.8</i> • <i>PL Section- 4</i> <u>Legal status:</u> <i>Prescription only medicine</i> <i>Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.</i> <u>Additional risk minimisation measures:</u> None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> None
Venous Thromboembolism (Important potential risk)	<u>Routine risk minimisation measures:</u> None <u>Legal status:</u> <i>Prescription only medicine</i> <i>Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.</i> <u>Additional risk minimisation measures:</u> None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> Adverse reaction follow-up Questionnaire <u>Additional pharmacovigilance activities:</u> None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Exposure during Pregnancy (Important potential risk)	<u>Routine risk minimisation measures:</u> - Guidance is given in the SmPC Section 4.6 to avoid the use of Steqeyma in pregnancy and use of effective methods of contraception are recommended during and 15 weeks after treatment. - PL Section- 2 <u>Legal status:</u> Prescription only medicine Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication. <u>Additional risk minimisation measures:</u> None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> None
Long-term safety in paediatric psoriasis patients 6 years and older (Missing information)	<u>Routine risk minimisation measures:</u> None <u>Legal status:</u> Prescription only medicine Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication. <u>Additional risk minimisation measures:</u> None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> None
Long-term impact on growth and development in paediatric psoriasis patients 6 years and older (Missing information)	<u>Routine risk minimisation measures:</u> None <u>Legal status:</u> Prescription only medicine Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication. <u>Additional risk minimisation measures:</u> None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term safety in adult patients with moderately to severely active Crohn's disease (Missing information)	<u>Routine risk minimisation measures:</u> None <u>Legal status:</u> <i>Prescription only medicine</i> <i>Restricted medical prescription by physicians experienced in the diagnosis and treatment of the applicable indication.</i> <u>Additional risk minimisation measures:</u> None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> None

2.4.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.5. Pharmacovigilance

2.5.1. 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.

2.5.2. 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.

2.6. Product information

2.6.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Stelara. The bridging report submitted by the applicant has been found acceptable.

2.6.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Steqeyma (ustekinumab) is included in the additional monitoring list as:

- it is a biological product that is not covered by the previous category and authorised after 1 January 2011.

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

Steqeyma (CT-P43) has been developed as a biosimilar to the reference medicinal product Stelara (ustekinumab). The applicant applied for the same indications as the reference medicinal product Stelara, except for the ulcerative colitis indication. These indications are:

- Plaque psoriasis (PsO)
- Paediatric plaque psoriasis (pPsO) in children and adolescents ≥ 6 to < 17 years of age
- Psoriatic arthritis (PsA)
- Crohn's disease (CD)

Steqeyma has been developed for subcutaneous and intravenous administration. The applicant only applied for 3 presentations: 45 mg solution for injection in prefilled syringe (glass), 90 mg solution for injection in prefilled syringe (glass) and 130 mg concentrate for solution for infusion (vial).

As Steqeyma is only available as 45 mg and 90 mg solution for injection in pre-filled syringe, it is not possible to administer Steqeyma to patients that require less than a full 45 mg dose. If an alternate dose is required, other ustekinumab products offering such an option should be used. This is adequately reflected in section 4.2 of the SmPC.

Quality aspects

The applicant has performed a sound and comprehensive analytical biosimilarity exercise, which can be expected to sufficiently reflect product variability of both the proposed biosimilar and the reference product. The chosen comparability approach of ± 3 SD for key biological attributes and a descriptive comparison of physicochemical attributes was found to be acceptable.

The quality attributes were shown to be highly similar between CT-P43 and EU Stelara using a large panel of analytical methods to characterise and compare the most relevant physicochemical and biological quality attributes of the ustekinumab molecule. Differences in C-terminal lysine variants, charge variants and glycan map profiles for CT-P43 compared to EU Stelara were identified, however, these have been described in detail, with any implications adequately justified.

Overall, biosimilarity with EU Stelara is considered to be demonstrated from a quality point of view.

Non-clinical aspects

The non-clinical development programme included *in vitro* primary pharmacodynamic (PD) studies and an *in vivo* 4-week repeat-dose toxicology study with toxicokinetic (TK) assessment in cynomolgus monkeys to compare Steqeyma with EU-approved Stelara. The conduct of repeated dose toxicity studies is not required for filing a biosimilar MAA in the EU and is usually not recommended (in accordance with EMA/CHMP/BMWP/403543/2010). Therefore, the *in vivo* data were assessed as complementary information.

The nonclinical development plan is in agreement with EMA guidelines for biosimilar products.

Clinical aspects

Comparability of Steqeyma to EU-Stelara in terms of PK, safety and immunogenicity was assessed in 2 phase 1 clinical studies in healthy subjects (Studies CT-P43 1.1 and CT-P43 1.2). Comparability in terms of efficacy, PK, safety and immunogenicity was assessed in a phase 3 study in patients with moderate to severe plaque psoriasis (Study CT-P43 3.1).

The applicant had originally planned a single Phase 1 study in healthy subjects, CT-P43 1.1, however following the observed PK data from this study, a second Phase 1 comparative PK study (CT-P43 1.2) in healthy subjects was subsequently planned.

The development plan was in agreement with EMA guidelines on development of biosimilar products.

3.2. Results supporting biosimilarity

Quality aspects

A large panel of analytical methods were used to characterise and compare the most relevant physicochemical and biological quality attributes of the ustekinumab molecule. The methods used are detailed in the biosimilarity exercise, Table 7.

Non-clinical aspects

In vitro comparability studies (discussed as part of the quality evaluation) did not show significant differences between Steqeyma and EU-Stelara. The toxicity profile of Steqeyma and EU-Stelara assessed in the 4-week study in cynomolgus monkeys was comparable.

Clinical Aspects

Pharmacokinetics

For Study CT-P43 1.1, biosimilarity of CT-P43 compared to EU-Stelara could not be demonstrated for the co-primary endpoint AUC_{0-inf} , as the 90% CI for the geometric mean ratio for AUC_{0-inf} (115.58 – 133.82) fell outside the acceptance range of 80.00% to 125.00%. However, post hoc analyses showed that this was related to an aggregation of effects related to protein content, immunogenicity and increased clearance associated with increased bodyweight and that bioequivalence could be shown when the results were corrected for these factors.

For Study CT-P43 1.2, the 90% CIs of the ratio of the geometric means for all PK primary endpoints (C_{max} and AUC_{0-inf}) were contained within the equivalence limits of 80% to 125%, with the CI for C_{max} being 95.14 – 107.76, and the CI for AUC_{0-inf} being 102.07 – 114.94.

In addition, a post-hoc pooled analysis of Study CT-P43 1.1 and Study CT-P43 1.2 suggested that the totality of the PK data showed that CT-P43 was equivalent to EU-Stelara with respect to the co-primary PK endpoints of C_{max} and AUC_{0-inf} (AUC_{0-inf} 109.55, 120.30, C_{max} 102.45, 112.48).

Efficacy

The primary efficacy endpoint in the comparative efficacy trial CT-P43 3.1 was the mean percent improvement from baseline in PASI score at Week 12. The equivalence test was conducted with patients who were administered at least one 45 mg of study drug and had never received 90 mg of study drug in Treatment Period I. The primary efficacy analysis was conducted on the FAS using an ANCOVA model. For the demonstration of efficacy, the point estimate and 95% CI for the estimate of treatment difference was entirely within the predefined equivalence margin of –15% to 15%, which demonstrated therapeutic equivalence between the CT-P43 and EU-Stelara groups in the mean percent

PASI score improvement from baseline at Week 12 (95% CI: [-2.29, 4.16] for the FAS and [-2.32, 4.07] for the PPS).

Safety

In the two Phase I studies in healthy male subjects, the overall safety profile was comparable between CT-P43 and reference EU and US Stelara. In both Phase I studies there were no TEAEs leading to death, no TEAEs leading to study drug discontinuation and no TEAEs of malignancy. In both studies the occurrence of hypersensitivity reactions was low overall and comparable between the treatment groups. There was a slightly higher occurrence of ISRs observed in Study CT-P43 1.2 for the CT-P43 treatment group, however on review this imbalance was not considered clinically meaningful. The number of subjects with at least one TEAE of infection were similar between treatment groups. In Study CT-P43 1.2 there were no TESAEs reported, whereas in Study CT-P43 1.1 there were 2 TESAEs in both CT-P43 and US Stelara groups. Only 1 TESAE in Study CT-P43 1.1 was considered related to study drug CT-P43 an event of Grade 2 abdominal pain lower, which resolved at end of study.

In Study CT-P43 3.1 in patients with moderate to severe plaque psoriasis, overall, no major differences in the safety profile between CT-P43 and EU-Stelara were observed. Some slight numerical imbalances were noted, but none were considered clinically meaningful or impacting upon the similarity assessment. The number of patients with at least 1 TESAE were balanced between the groups. In both Stelara maintenance and Switch to CT-P43 groups, only 1 patient in each group had a TEAE leading to study discontinuation. Only 1 patient had a TEAE of hypersensitivity reaction, Grade 3 headache in CT-P43 group. A slight imbalance in ISRs was seen in the CT-P43 groups but overall numbers were very low. The number of patients with at least 1 TEAE of infection/serious infection was generally balanced between the groups. There was a single occurrence of a Grade 5 TEAE of myocardial infarction considered unrelated to study drug in CT-P43 group for which other potential reasons were noted. One TEAE of malignancy with possible relationship to study drug was observed in CT-P43 group.

Overall, no major safety concerns or differences in the safety profile between CT-P43 and reference Stelara are observed from the assessment of CT-P43 studies.

Immunogenicity

In both healthy subjects and plaque psoriasis patients, the ADA and NAb incidences were lower in the CT-P43 treatment group compared to the EU-/US-Stelara treatment groups. The lower N-glycolylneuraminic acid (NGNA) content in CT-P43 compared to Stelara is a potential contributor to the lower immunogenicity of CT-P43. This difference in NGNA levels between CT-P43 and Stelara was expected given the use of different expression systems, Stelara being manufactured in the murine mouse myeloma cell line, Sp2/0 while CT-P43 is expressed in a Chinese hamster ovary cell line. In terms of the clinical impact, the applicant highlighted that in all CT-P43 clinical studies, the proportions of subjects who had at least 1 post-treatment ADA positive result showed that CT-P43 appeared less immunogenic than EU or US Stelara reference products. However, despite these differences and that antibodies to ustekinumab were associated with reduced serum concentrations, the applicant concluded that no significant impact on efficacy or safety was evident. The applicant also referred to a number of other biosimilar ustekinumab (candidates) in which similar findings of lower immunogenicity compared to reference was observed. The Guideline on Similar Biological Medicinal Products: non-clinical and clinical indicates that a lower immunogenicity for the biosimilar is a possible scenario, which would not preclude approval as a biosimilar. Overall, the CHMP noted the lower immunogenicity of CT-P43 was not found to impact the conclusion of biosimilarity assessment.

There was no apparent correlation between the presence of ADA and the occurrence of TEAE, TESAE, ISR or hypersensitivity reactions.

3.3. Uncertainties and limitations about biosimilarity

Quality aspects

The analytical similarity exercise is comprehensive. Minor differences in C-terminal lysine variants, charge variants and glycan map profiles for CT-P43 compared to EU Stelara were identified, however, these have been described in detail. These are not considered clinically significant and hence do not impact on the biosimilarity claim.

Non-clinical aspects

None

Clinical aspects

None

3.4. Discussion on biosimilarity

Quality

From a quality perspective, the analytical similarity exercise is comprehensive and supports a conclusion of biosimilarity.

Non-clinical

None

Clinical

Pharmacokinetics

In the PK study CT-P43 1.1 in healthy volunteers, biosimilarity of CT-P43 compared to EU-Stelara could not be demonstrated, as the 90% CI for the geometric mean ratio for AUC_{0-inf} fell outside the acceptance range of 80.00% to 125.00%, suggesting higher exposure with CT-P43 compared to EU-Stelara. However, the post-hoc root cause analyses conducted by the applicant confirm that acceptable differences in protein content and in the relative immunogenicity between the test and reference products in the study, along with an increased but probably random variability in the clearance seen in patients with increased bodyweight contributed significantly to this finding.

For the second PK study CT-P43 1.2 the primary PK endpoints were within pre-defined limits. In addition, a post-hoc pooled analysis, along with a tipping point sensitivity analysis of those results, confirmed that the totality of the PK data indicates the biosimilarity of the test and reference products.

Overall, the CHMP concludes that PK comparability/biosimilarity is established.

Efficacy

In the comparative efficacy trial CT-P43 3.1, CT-P43 showed similar efficacy as EU-Stelara in the primary and secondary efficacy endpoints as well as in the subgroup analyses. The equivalence of efficacy was demonstrated based on the primary endpoint and the comparable results for the secondary efficacy endpoints also supported the similarity of CT-P43 and EU-Stelara.

Safety and Immunogenicity

No relevant differences in safety were observed based on the available data between CT-P43 and EU-Stelara.

In terms of immunogenicity, subjects (both healthy volunteers and patients) treated with CT-P43 had lower ADA and nAb frequencies than subjects treated with Stelara. No immunogenicity related difference was observed in the safety profile of the two products.

3.5. Extrapolation of safety and efficacy

Similarity between Steqeyma and Stelara has been satisfactorily demonstrated, based on the totality of the data provided as part of the stepwise approach for biosimilars, including quality and functional characterisation, non-clinical studies and clinical efficacy and safety studies.

In this application, the applicant is seeking approval for CT-P43 for the same indications approved for the reference medicinal product Stelara, excluding ulcerative colitis.

Approval is sought for:

- 45 mg/0.5 mL (90 mg/mL) solution in a single-dose pre-filled syringe with safety guard for subcutaneous injection
- 90 mg/1 mL (90 mg/mL) solution in a single-dose pre-filled syringe with safety guard for subcutaneous injection
- 130 mg/26 mL (5 mg/mL) solution in a single-dose vial for intravenous infusion

The 45mg/0.5ml vial presentation for SC use was not applied for while it is required for body weight-based dosing of patients with paediatric PsO who weigh less than 60kg and who require less than a full 45mg dose. The product information therefore reflects on the unavailability of this vial presentation and refers to 'other ustekinumab products' that should be used if an alternative dose is required for subjects weighing less than 60kg in Section 4.2 of the SmPC and PL. This is acceptable.

The efficacy and safety study was conducted in patients with moderate, to severe plaque psoriasis patients (PsO). This selected study population represents the most sensitive population to demonstrate biosimilarity and is considered acceptable.

Additionally, ustekinumab's MoA is similar in each of the RMP's indications (PsO, paediatric PsO, PsA, CD) as the Th1 and Th17 cytokine pathways play a central role in their pathogenesis and are mediated by the ustekinumab targeted and inhibited IL-12 and IL-23.

Furthermore, the safety profile for ustekinumab is similar between these indications. Therefore, from the clinical point of view, extrapolation of the efficacy and safety data generated in PsO indication to all indications approved for the reference product is acceptable.

The extrapolation to the full range of indications (excluding ulcerative colitis) to align with the Stelara indications is acceptable. The extrapolation to full indications also implies extrapolation of data generated with subcutaneous administration to intravenous administration, which is also acceptable.

3.6. Additional considerations

Not applicable.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Steqeyma is considered biosimilar to Stelara. 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 Steqeyma is favourable in the following indications:

Plaque psoriasis

STEQEYMA is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1).

Paediatric plaque psoriasis

STEQEYMA is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies (see section 5.1).

Psoriatic arthritis (PsA)

STEQEYMA, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1).

Crohn's Disease

STEQEYMA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF α antagonist or have medical contraindications to such therapies.

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.

