

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761338Orig1s000

761338Orig2s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	BLA
Application Number	761338
Received Date	June 30, 2023
BsUFA Goal Date	June 30, 2024
Division/Office	Division of Dermatology and Dentistry /Office of Immunology and Inflammation (OII) in collaboration with the Division of Rheumatology and Transplant Medicine (DRTM)/OII and Division of Gastroenterology (DG)/OII
Review Completion Date	September 30, 2024
Product Code Name	CT-P43
Proposed Nonproprietary Name¹	Ustekinumab-stba
Proposed Proprietary Name¹	Steqeyma
Pharmacologic Class	IL12/23 BLOCKER
Applicant	Celltrion Inc.
Applicant Proposed Indication(s)	• Moderate to severe plaque psoriasis (PsO) in adult patients and pediatric patients 6 years of age and older who are candidates for phototherapy or systemic therapy; • Active psoriatic arthritis (PsA) in adult patients and pediatric patients 6 years of age and older; • Moderately to severely active Crohn's Disease (CD) in adults • Moderately to severely active Ulcerative Colitis (UC) in adults
Recommendation on Regulatory Action	Complete Response

¹Section 7 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

Table of Contents

Reviewers of Biosimilar Multidisciplinary Evaluation and Review	viii
Additional Reviewers of Application	viii
Glossary	x
Signatures	xii
1. Executive Summary	1
1.1. Product Introduction	1
1.2. Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act	2
1.3. Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment	2
1.4. Inspection of Manufacturing Facilities	2
1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product	3
1.6. Biosimilarity and Interchangeability Assessment	3
1.7. Conclusions on Approvability	6
2. Cross-Discipline Team Leader (CDTL) Introduction and Regulatory Background	7
2.1. Summary of Presubmission Regulatory History Related to Submission	7
2.2. Studies Submitted by the Applicant	12
3. Summary of Conclusions of Other Review Disciplines	14
3.1. Office of Pharmaceutical Quality (OPQ)	14
3.2. Devices	15
3.2.1. Center for Devices and Radiological Health (CDRH)	15
3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)	15
3.3. Office of Study Integrity and Surveillance (OSIS)	16
3.4. Office of Scientific Investigations (OSI)	17
4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations	17
4.1. Nonclinical Executive Summary and Recommendation	17
4.1.1. Nonclinical Residual Uncertainties Assessment	18
4.2. Product Information	18
5. Clinical Pharmacology Evaluation and Recommendations	20
5.1. Clinical Pharmacology Executive Summary and Recommendation	20
5.1.1. Clinical Pharmacology Residual Uncertainties Assessment	23
5.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product	23
5.3. Human Pharmacokinetic and Pharmacodynamic Studies	24

5.3.1.	Clinical Pharmacology Study Design Features	24
5.3.2.	Clinical Pharmacology Study Endpoints.....	26
5.3.3.	Bioanalytical PK Method and Performance.....	27
5.3.4.	PK Similarity Assessment	27
5.3.5.	Inspection of PK Similarity Study	28
5.3.6.	PK of CT-P43 and EU-Stelara in Subjects with Psoriasis	29
5.4.	Immunogenicity Studies	31
5.4.1.	Design features of the clinical immunogenicity assessment	32
5.4.2.	Immunogenicity endpoints	32
5.4.3.	Immunogenicity assay's capability of detecting the ADA and NAb in the presence of proposed product, U.S.-licensed reference product, and non-U.S.-licensed comparator product (as applicable) in the study samples.....	32
5.4.4.	Adequacy of the sampling plan to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA/NAb formation.....	32
5.4.5.	Incidence of ADA and NAb	33
6.	Statistical and Clinical Evaluation and Recommendations	41
6.1.	Statistical and Clinical Executive Summary and Recommendation.....	41
6.1.1.	Statistical and Clinical Residual Uncertainties Assessment.....	41
6.2.	Review of Comparative Clinical Studies with Statistical Endpoints	42
6.2.1.	STUDY CT-P43 3.1.....	42
6.3.	Review of Safety Data.....	64
6.3.1.	Methods	64
6.3.2.	Major Safety Results	74
6.3.3.	Additional Safety Evaluations.....	101
6.3.4.	Cross Discipline Team Leader Assessment.....	104
6.4.	Clinical Conclusions on Immunogenicity	111
6.5.	Risk in Terms of Safety or Diminished Efficacy of Switching Between Products and the Any Given Patient Evaluation (to Support a Demonstration of Interchangeability)	112
6.6.	Extrapolation	113
6.6.1.	DIVISION of RHEUMATOLOGY and TRANSPLANT MEDICINE (DRTM)	114
6.6.2.	Division of Gastroenterology	116
7.	Labeling Recommendations	118
7.1.	Nonproprietary Name.....	118
7.2.	Proprietary Name	118

7.3. Other Labeling Recommendations	119
8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure	119
9. Advisory Committee Meeting and Other External Consultations	119
10. Pediatrics	120
11. REMS and Postmarketing Requirements and Commitments	120
11.1. Recommendations for Risk Evaluation and Mitigation Strategies	121
11.2. Recommendations for Postmarket Requirements and Commitments	121
12. Comments to Applicant	121
13. Signatory Comments	122
14. Appendices	124
14.1. References	124
14.2. Financial Disclosure	127
14.3. Nonclinical Appendices	130
14.3.1. Nonclinical Pharmacology	130
14.3.2. Nonclinical Pharmacokinetics	130
14.3.3. General Toxicology	130
14.4. Clinical Pharmacology Appendices	131
14.4.1. Other PK similarity Study: Study CT-P43 1.1	131
14.4.2. Summary of Bioanalytical Method Validation and Performance	136
14.4.3. Other Clinical Pharmacology Information	140
14.5. Clinical Appendices	141

Table of Tables

Table 1: Summary and Assessment of Biosimilarity and Interchangeability.....	3
Table 2: CT-P43 Nonclinical Studies Submitted	12
Table 3: CT-P43 Clinical Studies Submitted	13
Table 4: List of Clinical and analytical sites inspected by OSIS	16
Table 5: Clinical Pharmacology Major Review Issues and Recommendations	20
Table 6: Summary of statistical analyses for assessment of PK similarity (Study CT-P43 1.2).....	23
Table 7: Statistical Summary of PK Parameters of Study Drug by Treatment Arm in Study CT-P43 1.2	28
Table 8: Serum Concentration ($\mu\text{g/mL}$) in Treatment period 1 in Study CT-P43 3.1	29
Table 9: Serum Concentration ($\mu\text{g/mL}$) in Treatment period 2 in Study CT-P43 3.1	30
Table 10: Immunogenicity Results in Study CT-P43 1.2 (Safety Set)	33
Table 11: Frequency of ADA and NAb by Dose (45 mg) in Study CT-P43 3.1 (Safety Set).....	34
Table 12: Frequency of ADA and NAb by Dose (90 mg) in Study CT-P43 3.1 (Safety Set).....	34
Table 13: Percent Change in C_{max} and AUC_{inf} by ADA Status (Study CT-P43 1.2).....	36
Table 14: Percent Change in Clearance and half-life by ADA Status (Study CT-P43 1.2)	37
Table 15: Serum Concentrations of Study Drug ($\mu\text{g/mL}$) by ADA Status in Study CT-P43 3.1 (treatment period 1).....	38
Table 16: Summary of TEAEs in PK similarity study CT-P43 1.2 by ADA status	39
Table 17: Summary of TEAEs in clinical efficacy study (CT-P43 3.1) by ADA status ...	39
Table 18: Summary of Percent Improvement from Baseline in PASI Score at Week 12 by ADA Status at Week 12 in Study CT-P43 3.1.....	40
Table 19: Number of Subjects in Statistical Analysis Sets	47
Table 20 Summary of Subject Disposition (Treatment Period I): ITT Set.....	48
Table 21 Summary of Subject Disposition (Treatment Period II) ITT – Treatment Period II Subset	49
Table 22 Demographics Characteristics: ITT Set	50
Table 23: Baseline Disease Characteristics in ITT Analysis Set	52
Table 24: Primary and Supportive Efficacy Results for the Primary Efficacy Endpoint (ANCOVA) – Multiple Imputation on Modified ITT Set (Primary) and PP Set (Supportive) ...	53
Table 25: Sensitivity Analysis Result for Primary Efficacy Endpoint:.....	53
Table 26: Sensitivity Analyses Results for Primary Efficacy Endpoint (ANCOVA):.....	54
Table 27: Comparison of Efficacy between Study CT-P43 3.1 and Stelara Studies	55
Table 28: The PASI Score: Modified ITT Set.....	56
Table 29: The PASI Score: Modified ITT – Treatment Period II Subset	57
Table 30: Percent Improvement from Baseline in PASI Score: Modified ITT Set.....	58
Table 31: Percent Improvement from Baseline in PASI Score:	60
Table 32: Proportion of PASI 50/75/90/100 Responders: Modified ITT Set	61
Table 33: Proportion of PASI 50/75/90/100 Responders	62
Table 34: Exposure to Study Medications, CT-P43 3.1 (Safety Analysis Set).....	66
Table 35 Demographics for CT-P43 3.1 Study.....	74
Table 36 Safety Summary for Study CT-P43 3.1 (Safety Analysis Set)	76

Table 37 Treatment-Emergent Serious Adverse Events (SAEs), CT-P43 3.1 (Safety Set).....	80
Table 38 Treatment-Emergent Adverse Events for $\geq 1\%$, CT-P43 3.1 (Safety Analysis Set).....	82
Table 39 Treatment-Emergent Adverse Events (Grade 3 or higher) in Study CT-P43 3.1	83
Table 40 Gastrointestinal Disorders SOC AEs during TP1, CT-P43 3.1 (Safety Analysis Set).....	85
Table 41 Treatment Emergent Adverse Event (TEAE) imbalances during Treatment Period 1 (TP1).....	87
Table 42 Treatment Emergent Adverse Event (TEAE) imbalances during Treatment Period 2 (TP2).....	89
Table 43 Neoplasms Benign, Malignant, or Unspecified for CT-P43 3.1.....	96
Table 44 TEAE Imbalances between CT-P43 Maintenance and EU-Stelara Maintenance (TP1 and TP2)	96
Table 45 Dropouts and Discontinuations for CT-P43 3.1	100
Table 46 Hypersensitivity Reaction-Like Adverse Events for CT-P43 3.1	102
Table 47 Baseline Weight for Study CT-P43 3.1	103
Table 48 Prior Immunosuppressant Use for Study CT-P43 3.1	103
Table 49: Summary of statistical analyses for assessment of PK similarity (Study CT-P43 1.1).....	132
Table 50: Statistical Summary of PK Parameters of Study Drug by Treatment Arm in Study CT-P43 1.1	133
Table 51. Protein content of clinical batches used in Study CT-P43 1.1 (Part 2)	134
Table 52: Immunogenicity Results in Study CT-P43 1.1 Part 2 (Safety Set).....	135
Table 53. Impact of ADA positivity (post-treatment ADA status) on C_{max} and AUC_{0-inf} in Study CT-P43 1.1 Part 2 (PK Set).....	135
Table 54. Summary of the bioanalytical method validation and in-study performance for measurement of CT-P43, US-Stelara and EU-Steara	137
Table 55 Demographics for CT-P43 1.1 Study.....	141
Table 56 Demographics for CT-P43 1.2 Study.....	142
Table 57 Treatment-Emergent Adverse Events for $\geq 2\%$, CT-P43 1.1.....	142
Table 58 Treatment-Emergent Adverse Events for $\geq 1\%$, CT-P43 1.2.....	144

Table of Figures

Figure 1. Study Schema for Study CT-P43 1.1	25
Figure 2. Study Schema for Study CT-P43 3.1	25
Figure 3. Study Schema for Study CT-P43 1.2	25
Figure 4. Mean (+/- SD) Serum Concentration of Study Drug (µg/mL) in Study CT-P43 1.2	27
Figure 5. Mean (+/- SD) Serum Concentration of Study Drug (µg/mL) up to EOS (Linear Scale) in Study CT-P43 3.1 (PK Set, PK-Treatment Period II Subset): Dose: 45 mg ...	30
Figure 6. Mean (+/- SD) Serum Concentration of Study Drug (µg/mL) up to EOS (Linear Scale) in Study CT-P43 3.1 (PK Set, PK-Treatment Period II Subset): Dose: 90 mg ...	31
Figure 7. Mean serum concentration of study drug in ADA positive subjects in Study CT-P43 1.2.....	35
Figure 8. Mean serum concentration of study drug in ADA negative subjects in Study CT-P43 1.2.....	36
Figure 9: Excerpt from the Applicant's Table for Reason for Study Discontinuation.....	69
Figure 10: Applicant's Table from 5.3.5.1, Study CT-P43 3.1 Final Clinical Study Report	70
Figure 11 Reason for Study Drug Discontinuation for (b) (6)	73
Figure 12: Mean (+/- SD) Serum Concentration of Ustekinumab (µg/mL) in Study CT-P43 1.1	132
Figure 13. Mean (+/- SD) Serum Concentration of study drug (µg/mL) by Batch in Study CT-P43 1.1	134

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² Dr. Sena Lee completed her review of the BLA and authored text in sections 1.1, 1.3, 2.1, 2.2, 3.4, 6.3.1, 6.3.2, 6.3.3, 14.1, 14.2, and 14.5 of the BMER. However, she left the Agency before the overall review of the BLA was completed. Therefore, her signature is not included below. The text that she authored was not altered after her departure, except for clarifications to introductory sections 1.1 and 1.3 and formatting changes.

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OBP = Office of Biotechnology Products

OPMA = Office of Pharmaceutical Manufacturing Assessment

OPDP = Office of Prescription Drug Promotion

OSI = Office of Scientific Investigations

OSE = Office of Surveillance and Epidemiology

DEPI = Division of Epidemiology

DMEPA = Division of Medication Error and Prevention Analysis

DRISK = Division of Risk Management

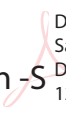
DPMH = Division of Pediatric and Maternal Health

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
AE	Adverse Event
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DIA	Division of Inspectional Assessment
DMC	Data Monitoring Committee
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
eCTD	Electronic Common Technical Document
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat
MOA	Mechanism of Action
NAb	Neutralizing Antibody

NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
OPQAI	Office of Product Quality Assessment III
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OPQR	Office of Pharmaceutical Quality Research
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation

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Biosimilar Multidisciplinary Evaluation and Review (BMER)

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APPEARS THIS WAY ON ORIGINAL

1. Executive Summary

1.1. Product Introduction

Celltrion (also referred to as “Applicant” in this review) has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for CT-P43 (non-proprietary name: ustekinumab-stba; proprietary name: STEQEYMA) as a proposed interchangeable biosimilar to US-licensed Stelara (US-Stelara, ustekinumab). CT-P43 is a recombinant human immunoglobulin isotype class G subclass 1 kappa monoclonal antibody (mAb) that belongs to the pharmacologic class of Interleukin -23 (IL-23) and Interleukin-12 (IL-12) antagonists.

The Applicant is seeking licensure for CT-P43 injection as follows:

- CT-P43, 45 mg/0.5 mL prefilled syringe (PFS) for subcutaneous use as interchangeable with US-Stelara injection 45 mg/0.5 mL PFS for subcutaneous use.
- CT-P43, 90 mg/mL PFS for subcutaneous use as interchangeable with US-Stelara injection 90 mg/mL PFS for subcutaneous use.
- CT-P43, 130 mg/26 mL single-dose vial for intravenous (IV) use as interchangeable with US-Stelara injection 130 mg/26 mL single-dose vial for IV use.

The Agency agreed to the Applicant’s deferral plan for the development of a 45 mg/0.5 mL single dose vial presentation for subcutaneous use for pediatric patients weighing less than 60 kg. The proposed strengths, dosage form, and routes of administration of CT-P43 are the same as those approved for US-Stelara.

Celltrion is seeking licensure of CT-P43 for the following indications for which US-licensed Stelara is approved:

- Moderate to severe plaque psoriasis (Ps) in adult patients and pediatric patients 6 years of age and older, who are candidates for phototherapy or systemic therapy
- Active psoriatic arthritis in adult patients and pediatric patients 6 years of age and older
- Moderately to severely active Crohn’s disease in adults
- Moderately to severely active ulcerative colitis in adults

Although the Division of Dermatology and Dentistry (DDD) is the lead division for this application and provided the written clinical review, clinical input pertaining to their respective indications was obtained from the Division of Gastroenterology (DG) and the Division of Rheumatology and Transplant Medicine (DRTM) during the course of the review.

1.2. Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

Not applicable

1.3. Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

CT-P43 is a recombinant human immunoglobulin isotype class G subclass 1 kappa (IgGk1) monoclonal antibody (mAb) that binds to the shared p40 subunit of interleukin-12 (IL-12) and interleukin-23 (IL-23) to block the IL-12- and IL-23-mediated signaling. Interleukin-23 and IL-12 are naturally occurring cytokines that are involved in inflammatory and immune responses in inflammatory conditions such as plaque psoriasis and psoriatic arthritis (among others). Interleukin-12 stimulates natural killer cells and drives the differentiation of CD4+ T cells toward the T helper 1 phenotype, while IL-23 induces and maintains the IL-17 pathway. CT-P43 has the same mechanisms of action as that of US-licensed Stelara to the extent known.

CT-P43 product is a sterile liquid solution available in a sterile, single-dose, preservative-free solution. CT-P43 injection is proposed as below:

For subcutaneous injection:

- 45 mg/0.5 mL in a pre-filled syringe (PFS)
- 90 mg/mL in a PFS

For IV infusion:

- 130 mg/26 mL (5 mg/mL) in a single-dose vial

Each strength of CT-P43 in each presentation is the same as that of US-licensed Stelara. CT-P43 also has the same dosage form and routes of administration as that of US-licensed Stelara. Additionally, the condition(s) of use for which the applicant is seeking licensure have been previously approved for US-licensed Stelara. The CT-P43 45 mg/0.5 mL and 90 mg/mL PFS are intended for the dosing regimens for the proposed indications in adults with PsO and PsA, the dosing regimens for the pediatric indications in children 6 years and older with PsO and PsA with body weight (BW) ≥ 60 kg, and the maintenance dosing for the indications of Crohn's disease and ulcerative colitis. . The single dose vial containing 130 mg/26 mL (5 mg/mL) is intended for the IV induction for the indications of Crohn's disease and ulcerative colitis .

1.4. Inspection of Manufacturing Facilities

All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage. Pre-license

inspections of the drug substance and drug product manufacturing facilities were waived.

1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

The Applicant provided adequate data to establish the scientific bridge to justify the relevance of data generated from the comparative clinical study CT-P43 3.1, which used EU-Stelara as the comparator, for the assessment of biosimilarity:

- The Office of Pharmaceutical Products (OPQ) CDER has determined, and I agree, that based on the data provided by the Applicant, the analytical component of the scientific bridge between CT-P43, US-licensed Stelara, and EU-approved Stelara was established.
- The Office of Clinical Pharmacology (OCP) has determined, that based on the data provided by the Applicant, the PK data established the PK component of the scientific bridge.

1.6. Biosimilarity and Interchangeability Assessment

Table 1: Summary and Assessment of Biosimilarity and Interchangeability

Comparative Analytical Studies³	
Summary of Evidence	• CT-P43 is highly similar to US-Stelara notwithstanding minor differences in clinically inactive components. • The strengths, dosage form and routes of administration of CT-P43 are the same as those of US-Stelara. • The analytical component of the scientific bridge between CT-P43, US-Stelara, and EU-Stelara was established to support the relevance of the data generated from studies using EU-Stelara as the comparator to the assessment of biosimilarity.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the product quality assessment.

³Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter therein for additional information regarding comparative analytical studies.

Animal/Nonclinical Studies	
Summary of Evidence	The information in the pharmacology/toxicology assessment supports the demonstration of biosimilarity.
Assessment of Residual Uncertainties	There are no residual uncertainties from the pharmacology/toxicology assessment.
Clinical Studies	
<i>Clinical Pharmacology Studies</i>	
Summary of Evidence	- PK similarity between CT-P43, US-Stelara and EU-Stelara was evaluated in healthy subjects (Study CT-P43 1.2) and supports a demonstration of no clinically meaningful differences between CT-P43 and US-Stelara. - PK similarity between CT-P43, EU-Stelara and US-Stelara provides the PK component of the scientific bridge to support the relevance of comparative clinical data generated using EU-Stelara in Study CT-P43 3.1 to the assessment of biosimilarity. - The incidence of anti-drug antibodies (ADA) and neutralizing antibody (Nab) formation for CT-P43 was numerically lower compared to those of US-Stelara and EU-Stelara in healthy subjects in the PK similarity study (Study CT-P43 1.2) and was also numerically lower compared to that of EU-Stelara in subjects with psoriasis in the comparative clinical study (Study CT-P43 3.1). - In the comparative clinical study (Study CT-P43 3.1), a slight increase in ADA response rate was noted following switching of treatment to CT-P43 from EU-Stelara compared to EU-Stelara maintenance group in 90 mg dose group. - However, the numerical differences in ADA and Nab incidences in Studies CT-P43 3.1 and 1.2 are not considered to be clinically significant and do not preclude the conclusion of no clinically meaningful differences between CT-P43 and US-Stelara, as the systemic exposure between the treatment groups are comparable.

Assessment of Residual Uncertainties	There are no residual uncertainties from a clinical pharmacology perspective.
Additional Clinical Studies	
Summary of Evidence	- In Study 3.1, there were no meaningful differences in terms of efficacy between CT-P43 and EU-Stelara. The frequency of treatment emergent adverse events, serious events, and events leading to discontinuation of study drug had no meaningful differences between treatment arms. - Given that the scientific bridge was established (based on the analytical and PK comparisons) between CT-P43, US-Stelara, and EU-Stelara to justify the relevance of the data generated with EU-Stelara as the comparator, the collective evidence from submitted clinical studies, including the comparative clinical study 3.1, supports a demonstration of no clinically meaningful differences between CT-P43 and US-Stelara.
Assessment of Residual Uncertainties	There are no residual uncertainties from the clinical or statistical perspective.
Switching Study	
Summary of Evidence	- FDA determined that a switching study is not necessary to support a demonstration of interchangeability for CT-P43. - The Applicant has provided adequate data and information to support a demonstration that the risk in terms of safety or diminished efficacy of alternating or switching between use of CT-P43 and US-Stelara is not greater than the risk of using US-Stelara without such alternation or switch.
Assessment of Residual Uncertainties	There are no residual uncertainties from the clinical perspective.
Any Given Patient Evaluation	

Summary of Evidence	The analytical data and clinical data support a demonstration that CT-P43 can be expected to produce the same clinical result as that of US-Stelara in any given patient. The Applicant has provided adequate data and information to support a demonstration that CT-P43 can be expected to produce the same clinical result as that of US-Stelara in any given patient.
Assessment of Residual Uncertainties	There are no residual uncertainties from the clinical perspective.
Extrapolation	
Summary of Evidence	- DDD, DG, and DRTM teams have determined that the Applicant has provided adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of data and information, including clinical data from the studied population (PsO), to support licensure of CT-P43 as an interchangeable biosimilar, under section 351(k) of the PHS Act, for the following indications for which US-licensed Stelara has been previously approved: - Moderate to severe plaque psoriasis in adult patients and pediatric patients 6 years of age and older who are candidates for phototherapy or systemic therapy - Active psoriatic arthritis in adult patients and pediatric patients 6 years of age and older - Moderately to severely active Crohn's disease in adults - Moderately to severely active ulcerative colitis in adults
Assessment of Residual Uncertainties	There are no residual uncertainties regarding the extrapolation of data and information to support licensure of CT-P43 as an interchangeable biosimilar to US-Stelara for the above indications.

1.7. Conclusions on Approvability

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that CT-P43 is highly similar to US-licensed Stelara, notwithstanding minor

differences in clinically inactive components, and that there are no clinically meaningful differences between CT-P43 and US-licensed Stelara in terms of the safety, purity, and potency of the product. The data and information provided by the Applicant are sufficient to demonstrate that CT-P43 can be expected to produce the same clinical result as US-licensed Stelara in any given patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of CT-P43 and US-licensed Stelara is not greater than the risk of using US-licensed Stelara without such alternation or switch. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that CT-P43 may be approved for each of the following indications for which US-licensed Stelara has been previously approved and for which the Applicant is seeking licensure of CT-P43:

- Moderate to severe plaque psoriasis in adult patients and pediatric patients 6 years and older, who are candidates for phototherapy or systemic therapy.
- Active psoriatic arthritis in adult patients and pediatric patients 6 years and older
- Moderately to severely active Crohn's disease in adults
- Moderately to severely active ulcerative colitis in adults

However, data submitted in this application are not sufficient to support a conclusion that the manufacture of CT-P43 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. Multiple product quality deficiencies including inadequate control of drug product, and insufficient data to support sterility assurance of the CT-P43 130 mg/26 mL (5 mg/mL) single-dose vial drug product have been identified and listed in the OPQ executive summary. Therefore, the FDA review team recommended a Complete Response for this application, and the CDTL and the Division Signatory agree with that recommendation. The Complete Response Letter will outline the deficiencies and the information and data required to address the deficiencies.

Author:

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2. Cross-Discipline Team Leader (CDTL) Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

Celltrion opened IND 146085 on October 19, 2019 with a request for a Biosimilar Initial Advisory Meeting to discuss the development of CT-P43 as a proposed biosimilar product to U.S.-Stelara (ustekinumab). On June 30, 2023, the Applicant submitted a biologics license application (BLA) under Section 351(k) of the Public Health Service

(PHS) Act. The Division had several meetings and communications with the Applicant during the development program of CT-P43. Key Agency recommendations are highlighted below:

- A Biosimilar Initial Advisory Meeting Request was denied on November 7, 2019, because there were insufficient preliminary analytical similarity data between the proposed biosimilar and the US-licensed reference product to determine whether the submission is appropriate as a proposed biosimilar biological product under the section 351(k) of the Public Health Service Act (PHS Act).
- A Biosimilar Biological Product Development (BPD) Type 2 Meeting for Pre-IND 146085 was held on February 26, 2020 and focused on the overall development plan for CT-P43 and analytical data needed to support the development of CT-P43 as a proposed biosimilar to US-licensed Stelara. This discussion included a proposed clinical study design to establish biosimilarity. The following were recommended by the Agency:
 - Conduct analytical assays to assess whether the observed differences between CT-P43 and US-Stelara in terms of oxidation, glycosylation, glycation, etc. have an impact on biological activity.
 - Conduct a comprehensive user-related risk analysis to determine the need for a human factors (HF) validation study. If seeking an exemption for an HF validation study, submit the risk analysis, comparative analyses, and justification for not submitting the HF validation study.
 - Conduct risk assessment to determine the critical quality attributes (CQAs) of US-Stelara that could be impacted by differences in formulation, strength, and container closure system and to determine whether testing of additional US-Stelara strengths and presentations is needed.
 - Discontinue further dosing subjects with <PASI 50 at Week 12 and subjects with <PASI 75 at Week 28.
 - Clinical efficacy equivalence margins should be ± 10 , not ± 15 , for the primary endpoint of per cent improvement from baseline Psoriasis Area and Severity Index (PASI) at Week 12 and that the Investigator Global Assessment (IGA) scale should be a 5-point, not 6-point, scale, as “marked” and “severe” belong in the same severity category.
- On June 3, 2020, as Special Protocol Assessment, the Applicant proposed that subjects weighing ≤ 100 kg will be enrolled for at least 70% of the total enrollment. The Agency recommended the following:
 - Set no limitation on the proportion of subjects eligible for inclusion based on weight ≥ 100 kg (and who should receive a total dose of 90 mg) as these subjects may represent a more sensitive population.
 - Subjects with <PASI 50 at Week 12 and subjects with <PASI 75 at Week 28 should not be further dosed.
 - For statistical analysis, the primary population should be the Full Analysis Set (FAS), defined as all randomized subjects dispensed study product regardless

- of whether the subjects have any post-baseline assessments.
- Pre-specify in the statistical analysis plan (SAP) the complete details of the handling of the missing data.
 - Questions regarding immunogenicity assays will be addressed in a BPD Type 2 meeting.
- On July 15, 2020, in a Biosimilar Biological Product Development (BPD) Type 2, Written Response Only interaction, the Agency reiterated the HF validation study recommendations from the 2/26/2020 meeting.
 - On September 23, 2020, in a Biosimilar Biological Product Development (BPD) Type 2, Written Response Only interaction, the Agency stated that the proposed multi-tiered approach for the immunogenicity testing in Study CT-P43 3.1 appeared reasonable.
 - On March 17, 2021, as Human Factors Validation Study Advice, after consulting DMEPA, the Agency sent a letter stating that a Human Factors (HF) Validation Study was “not required.”
 - On June 23, 2021, in a Biosimilar Biological Product Development (BPD) Type 2, Written Response (Meeting Cancelled) interaction, the Agency stated the following:
 - The adequacy of the number of independent CT-P43 lots included in the statistical analysis for each assay in the CAA will be a review issue. Include a justification for the number of lots used in each assay taking into consideration variability of each assay.
 - Define and justify similarity criteria that will be used in the CAA for the 45 mg/ 0.5 mL vial and 130 mg/ 26 mL vial for attributes that may be affected by differences in the container closure, strength and formulation.
 - The adequacy of the risk assessments and comparability data would be a review issue. (Celltrion had indicated that more lots of the 45 mg/ 0.5 mL PFS presentations would be included in the CAA, compared to the 90 mg/ 1 mL PFS and the 45 mg/ 0.5 mL SC vial presentations for US-Stelara and CT-P43.)
 - For most critical quality attributes, use orthogonal methods to confirm the results included in the CAA.
 - Identify charge variant species and determine their impact on biological activity and pharmacokinetics.
 - In CAA, include analysis of 100% of amino acid sequence, assessment of FcγRIIIb binding, assessment of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).
 - In establishing the analytical portion of the scientific bridge, include in the CAA the CT-P43, US-Stelara, and EU-Stelara lots used in the clinical studies.
 - In establishing the analytical portion of the scientific bridge, include three pair-wise comparisons: between EU-Stelara and US-Stelara, between EU-Stelara

- and CT-P43, and between US-Stelara and CT-P43.
- Three process validation lots of CT-P43 45 mg/0.5 mL PFS and one process validation lot of CT-P43 90 mg/ 1 mL PFS may not be sufficient. Recommend manufacturing three 90 mg/1 mL PFS PPQ lots.
 - Fill volume should be consistent with USP <1151> guidelines for vial presentations and should be supported by extractable/deliverable experimental data.
 - In comparative stability and forced degradation studies, provide a justification for the attributes that will be evaluated. Include an evaluation of rate of degradation and type of degradation species. Also, provide a scientific justification for the stress conditions used in the forced degradation studies.
 - The Agency (b) (4) recommended using a multiple imputation approach as the primary method of handling missing data with supportive analyses that use alternate assumptions and a tipping point analysis. The Agency also recommended including complete details regarding these methods in the protocol/statistical analysis plan to fully pre-specify analyses.
 - The Agency reiterated the 6/2020 recommendation of defining the Full Analysis Set (FAS) as all randomized subjects dispensed study product regardless of whether the subjects have any post-baseline assessments.
- On July, 2021, in an FDA Letter to the Applicant regarding HF validation study protocol, the Agency informed the Applicant to submit a new HF validation study protocol review request for their pre-filled syringe (PFS), because the prior submission was missing the analysis of hazards and risks in the User Related Risk Analysis. The Applicant declined to request a new review, citing the previous letter from the Agency stating that a Human Factors Validation Study was not required.
 - On December 13, 2021, in a Biosimilar Biological Product Development (BPD) Type 2 Meeting, the Applicant proposed to submit a Clinical Study Report (CSR) for Study CT-P43 3.1 up to Week 28 with an equivalence margin of [-15%, +15%] using 95% confidence interval(CI) for the primary efficacy endpoint, the equivalence margin for global submission. For the US application, the Applicant proposed to submit the CSR but include the efficacy data analyzed with a margin of [-10%, +10%] using 90% CI agreed upon by the FDA in the Clinical Overview and Summary of Clinical Efficacy. The Agency stated that CSR should include the analyses agreed upon by FDA and the Applicant as previously conveyed in the Special Protocol Assessment-No Agreement (June 3, 2020) and Study May Proceed (December 16, 2020) letters. (b) (4)
- On February 14, 2022, in a Biosimilar Biological Product Development (BPD) Type 2, Written Response Only interaction, the Agency stated that the human IL-12

reporter assay appeared suitable.

- On September 14, 2022 at a Biosimilar Biological Product Development (BPD) Type 2 Meeting, the Agency recommended the following:
 - The Applicant's three-way pharmacokinetics (PK) study to assess PK similarity between CT-P43, US- and EU-Stelara (Study CT-P43 1.1 Part 2) did not meet the upper bounds of the 90% CIs for AUC_{0-inf} were over the 125% acceptance range between CT-P43 and US-Stelara/EU-Stelara. The Agency stated that the Applicant may conduct a new 3-way PK similarity study, but the Applicant must provide a justification to support the acceptability of the data from the new study by providing details of the difference in quality attributes of the products used in the old and new PK similarity studies.
 - The Applicant proposed to include two strengths of CT-P43 (45 mg and 90 mg) presented in PFS, and for the initial BLA, proposed to exclude indication for pediatric psoriasis who weigh <60kg but include all the other approved indications of Stelara, including CD and UC induction. Given that the dosing regimen for the treatment of CD and UC includes a single IV dose, followed by continued treatment with the subcutaneous (SC) presentation, the Agency recommended submission of data for the 130 mg vial presentation at the time of the initial BLA submission for ease of use in the clinical setting.
 - The Agency recommended that the Applicant 1) demonstrate comparability between drug product (DP) lots manufactured at the clinical and the commercial manufacturing sites, (b) (4) Celltrion Pharm. Inc., Republic of Korea, respectively, and 2) verify that each of the proposed CT-P43 lots used in the CAA are independent lots made from different DS lots and made from independent fill activities or identify if any lots are not independent and are linked to the same drug substance (DS) lot. At the meeting, the Agency cautioned the Applicant regarding using a limited number of lots to demonstrate comparability between the two strengths, 45 mg/0.5 mL and 90 mg/mL PFS, but the Agency agreed that the number of lots would be sufficient to meet the minimal number of lots for the CAA.
- On January 27, 2023 in a Biosimilar Biological Product Development (BPD) Type 2, Written Response (Meeting Cancelled) interaction, the Agency found the Applicant's proposed study design for establishing interchangeability between CT-P43 and US-Stelara reasonable with the following exceptions and recommendations:
 - 1) PASI 50 is not acceptable as a secondary endpoint.
 - 2) In addition to analyzing efficacy endpoints in the Efficacy Set defined as all subjects who are randomized and received at least 1 dose of the study drug during the Switching Period, analyze efficacy endpoints in the Per Protocol Set.
 - 3) Provide details in Statistical Analysis Plan.

4) Provide justification for an estimation of 70% coefficient variant (CV).

The Agency cautioned that uncertainties remained from the CAA and PK data from the Study CT-p43 1.1 Part 2.

On September 1, 2023, the FDA sent an advice/information request letter to the Applicant's IND sharing its updated scientific thinking that a switching study would generally be considered unnecessary to support a demonstration of interchangeability for proposed ustekinumab interchangeable biosimilar products.

On November 20, 2023, the Applicant amended 351(k) BLA-761338 to support the claim for CT-P43 as a proposed interchangeable biosimilar product to US-licensed Stelara and stated that a switching study will not be conducted to demonstrate the interchangeability of CT-P43. The Applicant cited the requirements in section 351(k)(4) of the Public Health Service Act and stated that the Module 2 clinical sections (especially, Section 2.7.2.4) and Module 3 quality sections supported the interchangeability claim.

- On February 16, 2024, under IND 146085, the Applicant submitted an amendment to the iPSP Version 5.0 to include the 45 mg/0.5 ml vial presentation.

2.2. Studies Submitted by the Applicant

Refer to the Product Quality review, including the Comparative Analytical Assessment (CAA) Chapter for information regarding comparative analytical studies provided to support a demonstration of biosimilarity.

Table 2: CT-P43 Nonclinical Studies Submitted

Study Title	Study Number	Species	Number Per Treatment Arm	Study Duration	Route of administration /Dose
Animal Studies					
CT-P43 and Stelara: A 4-week once weekly subcutaneous injection toxicity and toxicokinetics study	8416958	Cynomolgus monkey	3/sex/group	4 weeks	Subcutaneous injection / 45 mg/kg

Study Title	Study Number	Species	Number Per Treatment Arm	Study Duration	Route of administration /Dose
in cynomolgus monkeys					

Table 3: CT-P43 Clinical Studies Submitted

Type of Study	Study Design and Type of Control	Study Objectives	Study Population	Duration of Treatment
PK similarity CT- P43 1.1	Randomized, double-blind, 3-arm, parallel group, single dose study to compare the PK and safety of CT-P43, EU-Stelara and US- Stelara in healthy male subjects CT-P43, EU-Stelara or US- Stelara 45 mg (45 mg/0.5 ml), a single PFS SC injection of study drug	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)	Healthy male volunteers Part 1: Randomized: 30 - CT-P43: 14 - EU-Stelara: 16 Part 2: Randomized: 241 - CT-P43: 80 - EU-Stelara: 82 - US-Stelara: 79	Up to Day 127
PK similarity CT- P43 1.2	Randomized, double-blind, 3-arm, parallel group, single dose study to compare the PK and safety of CT-P43, EU-Stelara and US- Stelara in healthy Japanese male subjects CT-P43, EU-Stelara or US-Stelara 45 mg (54mg/0.5ml), a single PFS SC injection of study drug	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 additional PK, safety and immunogenicity of CT-P43, EU-Stelara and US-Stelara in healthy Japanese male subjects up to Day 113 (Week 16)	Healthy Japanese male volunteers Randomized:331 - CT-P43: 114 - EU-Stelara: 110 - US-Stelara: 107	Up to Day 113

Biosimilar Multidisciplinary Evaluation and Review (BMER)

Comparative efficacy and safety CT- P43 3.1	Double-blind, randomized, active controlled, parallel group study to compare efficacy and safety of CT-P43 and EU-Stelara in patients with moderate to severe plaque psoriasis CT-P43 or EU-Stelara Patients who weigh ≤100kg: 45 mg (1 injection of 45mg/0.5ml) of study drug by SC injection via PFS Patients who weigh >100kg: 90 mg (2 injections of 45 mg/0.5 ml) of study drug by SC injection via PFS Patients receive an initial dose of study drug 45 or 90mg administered subcutaneously, followed by another dose 4 weeks later, and then every 12 weeks thereafter up to Week 40.	Primary: To demonstrate CT- P43 is equivalent to EU-Stelara in terms of efficacy as determined by the mean percent improvement from baselines in PASI score at Week 12. Secondary: To evaluate efficacy, PK, quality of life, and overall safety including immunogenicity up to Week 52	Adults with moderate to severe plaque psoriasis Randomized: 509 - CT-P43: 256 - EU-Stelara: 253	Up to Week 52
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Source: CTD Module 5, Section 5.2

Authors:

Sena Lee, MD, PhD
Clinical Reviewer

Amy Voitach, DO, MS
Clinical Team Leader

3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

OPQ is not recommending approval of BLA 761338 for CT-P43 manufactured by Celltrion, Inc. The data submitted in this application are not sufficient to support the conclusion that the manufacture of CT-P43 is well-controlled and leads to a product that is pure, safe, and potent. Multiple product quality deficiencies including inadequate control of drug product and insufficient data to support sterility assurance of the CT-P43 130 mg/26 mL (5 mg/mL) single-dose vial drug product have been identified and listed in the OPQ executive summary. From an OPQ perspective, this BLA is not

recommended for approval in its present form until the product quality deficiencies are satisfactorily resolved.

The comparative analytical data support a demonstration that CT-P43 is highly similar to US-licensed Stelara, notwithstanding minor differences in clinically inactive components. CT-P43 has the same strengths as U.S.-Stelara. In addition, the Applicant adequately established the analytical component of the scientific bridge which supports the relevance of the data generated from clinical studies using EU-Stelara as the comparator for the assessment of biosimilarity.

3.2. Devices

CT-P43 injection is a sterile liquid solution with the following proposed strengths in a prefilled syringe (PFS) with a safety guard (PFS-S):

- Injection: 45 mg/0.5 mL in a single-dose PFS
- Injection: 90 mg/mL in a single-dose PFS

The CT-P43 PFS container closure system consists of a 1 mL Type ^{(b) (4)} glass syringe with a staked stainless steel needle, closed with an elastomeric needle shield, and a ^{(b) (4)} elastomeric plunger-stopper. The PFS-S is fitted with a safety guard, a single-use, disposable device to protect users from needle stick injury after injection.

3.2.1. Center for Devices and Radiological Health (CDRH)

CDRH reviewed the safety feature of the proposed combination product. The safety device is a cleared device being used within its indications for use. CDRH recommends approval.

3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)

The Applicant submitted a use-related risk analysis (URRA) and comparative analyses under IND 146085 for CT-P43 PFS, a proposed biosimilar to US-licensed Stelara. DMEPA reviewed the URRA and comparative analyses and determined that no additional data from a human factors (HF) validation study was needed to support interchangeability with US-licensed Stelara. In this marketing application, the Applicant included the same URRA and comparative analyses they submitted under their IND. The Applicant confirmed that the user-interface is identical to the user interface evaluated under their IND. As such, DMEPA maintains that the Applicant does not need to submit HF validation study results with marketing application. DMEPA has no HF recommendations.

3.3. Office of Study Integrity and Surveillance (OSIS)

The Division requested that the Office of Study Integrity and Surveillance (OSIS) conduct clinical and analytical site inspections at the sites in Table 4. All of the sites participated in Study CT-P43 1.2 (PK similarity study). OSIS has inspected all three sites^{4,5}. See Table 4 for their conclusions. For additional information refer to Section 14.4.3 Other clinical pharmacology information section.

Table 4: List of Clinical and analytical sites inspected by OSIS

Name, Address, Phone number, email, fax#	Protocol ID/Clinical Site #	No. of Subjects	Purpose	Date of OSIS Review	Comments/ Conclusion
Kitasato University, Kitasato Institute Hospital, 5-9-1 Shirokane, Minato-ku, Tokyo, Japan Phone: +81 3-3444-6161	CT-P43 1.2/ Clinical site# 4304	107	Clinical site inspection	January 15-19, 2024	No objectionable conditions were observed
Medical Corporation Heishinkai OPHAC Hospital 4-1-29 Miyahara, Yodogawa-ku, Osaka-shi, Osaka, Japan	CT-P43 1.2/ Clinical site# 4305	106	Clinical site inspection	January 22-25, 2024	No objectionable conditions were observed

⁴ OSIS Memorandum dated April 1, 2024; DARRTS ID: 5356738

⁵ OSIS Memorandum dated February 29, 2024; DARRTS ID: 5337653

(b) (4)	CT-P43 1.2	..	Bioanalytical site inspection	(b) (4) Minor findings regarding (b) (4) for Study CT-P43 1.2. However, OSIS concluded that this finding did not impact the reliability of the bioanalytical method and study results
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3.4. Office of Scientific Investigations (OSI)

The Division requested that the Office of Scientific Investigation (OSI) to conduct site inspections at select sites for the Study CT-P43 3.1. Two clinical investigators (Drs. Jaworski and Daniluk) were selected for clinical inspections. Dr. Jaworski's site (Site 2510) had the highest enrollment for the study. Dr. Daniluk (Site 2511) was previously inspected in 2017. The inspections did not find significant concerns regarding the oversight of the clinical trial or GCP or regulatory compliance. Based on the results of these inspections, data generated by the inspected clinical investigators appear acceptable in support of the proposed indication.

The examples of inaccurate or inappropriate reporting of adverse events discussed in **Quality and Integrity of Safety Data** were from sites not inspected by the OSI: Sites 2502, 2503, 2519, and 5403.

Author:

Sena Lee, MD, PhD
Clinical Reviewer

CDTL comment: The inspection provides a reasonable sampling of the data and is sufficient to understand whether there were significant data integrity issues that would impact the Agency's assessment. The inconsistencies or omissions in medical history collection, safety-event follow-up, or adverse event coding identified by the primary reviewer appear to be minor, inconsequential, and consistent with errors that typically occur in clinical trial data collection. This reviewer does not concur that the inconsistencies identified by the primary reviewer indicate a significant issue with data integrity. Refer to sections 6.3.4 and 8 for further detail.

4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

The FDA has determined that animal testing is unnecessary to support a demonstration of biosimilarity between CT-P43 and US-Stelara. Refer to the OPQ section for detailed

documentation (Section 3.1). From a nonclinical perspective, because the toxicity of ustekinumab products, barring differences in clinical pharmacokinetic (PK) parameters, is a direct function of their affinity to bind to the shared p40 subunit of interleukin-12 (IL-12) and interleukin-23 (IL-23) to block the IL-12- and IL-23-mediated signaling, the comprehensive battery of in vitro cell-free and cell-based studies are considered more sensitive than animal studies in detecting differences, between CT-P43 and US-Stelara. In the absence of specific pharmacokinetic, physicochemical, or other identifiable concerns, in vivo animal studies are not anticipated to provide additional meaningful information to inform the evaluation of toxicity. Animal studies with CT-P43 are not required to support this 351(k) application.

However, the applicant conducted a 4-week toxicity study in monkeys using CT-P43 and EU-approved Stelara (EU-Stelara) and submitted the study report to the BLA. This study is reviewed in Section 14 for completeness. The study results showed that the toxicity and toxicokinetic (TK) profiles of CT-P43 and EU-Stelara were similar.

In summary, no animal studies with CT-P43 and US-Stelara were needed to support this 351(k) application and the results of the in vitro studies support a demonstration of biosimilarity.

4.1.1. Nonclinical Residual Uncertainties Assessment

There are no nonclinical residual uncertainties.

4.2. Product Information

Product Formulation

The composition of the CT-P43 product (pre-filled syringe and vial) is shown in the two tables below.

Composition of the CT-P43 pre-filled syringe product (for subcutaneous administration):

Ingredient	Quantity ¹ /Syringe		Function	Grade
	CT-P43 45 mg	CT-P43 90 mg		
CT-P43 (ustekinumab)	45 mg	90 mg	Active ingredient	In-house
(b)(4) histidine	0.18 mg	0.36 mg	(b)(4)	Ph. Eur., USP
L-histidine Monohydrochloride Monohydrate	0.46 mg	0.91 mg		Ph. Eur.
Surcrose	38.00 mg	76.00 mg		NF, Ph. Eur.
Polysorbate 80	0.02 mg	0.04 mg		NF, Ph. Eur.
Water for Injection	Q.S. to 0.5 mL	Q.S. to 1.0 mL		Ph. Eur., USP

NF: National Formulary, Ph. Eur.: European Pharmacopeia, Q.S: Quantum Satis, USP: United States Pharmacopeia

¹ The amount of each component per syringe is nominal value.

Composition of the CT-P43 vial product (for intravenous administration):

Ingredient	Quantity ¹	Function	Grade
	CT-P43 130 mg		
CT-P43 (ustekinumab)	130 mg	Active ingredient	In-house
(b) (4) Histidine	9.36 mg	(b) (4)	Ph. Eur., USP
L-Histidine monohydrochloride monohydrate	23.66 mg		Ph. Eur.
EDTA disodium salt (b) (4)	(b) (4) mg		Ph. Eur., USP
(b) (4) Methionine	10.56 mg		Ph. Eur., USP
Sucrose	1,976.00 mg		NF, Ph. Eur.
Polysorbate 80	10.37 mg		NF, Ph. Eur.
Water for Injection	Q.S. to 26 mL		Ph. Eur., USP

NF: National Formulary, Ph. Eur.: European Pharmacopeia, Q.S: Quantum Satis, USP: United States Pharmacopeia

¹ The amount of each component per vial is nominal value.

Comments on Excipients

Ingredient	Quantity per unit					
	CT-P43 45 mg PFS	Stelara 45 mg PFS	CT-P43 90 mg PFS	Stelara 90 mg PFS	CT-P43 130 mg vial	Stelara 130 mg vial
CT-P43 or ustekinumab	45 mg	45 mg	90 mg	90 mg	130 mg	130 mg
L-histidine monohydrochloride monohydrate	0.46 mg	0.5 mg	0.91 mg	1 mg	23.66 mg	27 mg
sucrose	38 mg	38 mg	76 mg	76 mg	(b) (4) mg	2210 mg
Polysorbate 80	0.02 mg	0.02 mg	0.04 mg	0.04 mg	10.37 mg	10.4 mg
(b) (4)						

Source: FDA-generated table

(b) (4)

methionine in the proposed CT-P43 130 mg/26 mL vial is within the ranges that are found in the inactive ingredient database. There are no concerns for the excipients at the proposed levels.

Comments on Impurities of Concern

There are no concerns for potential impurities contained in CT-P43.

Authors:

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5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

Table 5. Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	- PK similarity between CT-P43 and US-Stelara was demonstrated in healthy subjects (Study CT-P43 1.2) and supports a demonstration of no clinically meaningful differences between CT-P43 and US-Stelara. - The three way PK similarity established between CT-P43, EU-Stelara and US-Stelara in Study CT-P43 1.2 provides the PK component of the scientific bridge to support the relevance of using EU-Stelara in the comparative clinical study (Study CT-P43 3.1).
Pharmacodynamics	Not applicable
Immunogenicity	- The incidence of anti-drug antibodies (ADA) and neutralizing antibody (NAb) formation for CT-P43 was numerically lower (16.2% for ADA and 12.6% for NAb) compared to those of US-Stelara (39.6% for ADA and 15.1% for NAb) and EU Stelara (44.4% for ADA and 16.7% for NAb) in healthy subjects in the PK similarity study (Study CT-P43 1.2). - In study CT-P43 3.1, the immunogenicity results in both dose groups (45 mg and 90 mg) indicate that CT-P43 appears to be less immunogenic compared to EU-Stelara. In the

	45 mg dose group, 21 (10.7%) and 42 (21.1%) subjects in the CT-P43 and EU-Stelara groups, respectively, were found to have at least one ADA positive result after exposure to the study drug up to Week 16. In 90 mg group, 5 (8.5%) and 19 (35.2%) subjects in the CT-P43 and EU-Stelara groups, respectively, exhibited at least one ADA positive result after exposure to the study drug at end of treatment period I (Week 16) (prior to re-randomization to start switching treatment). - At the end of treatment period II (Week 52) (single transition arm, also referred to as “Switching arm”), in 45 mg dose group, the ADA response rate in EU-Stelara maintenance and switching arm were 33.7% and 30.9%, respectively. In contrast to 45 mg group, a numerical slight increase in ADA response rate was observed in switching arm in 90 mg group. At the end of treatment period II, in 90 mg dose group, the ADA response rate in EU-Stelara maintenance and switching arm were 37% and 44.4%, respectively. - The numerical difference in ADA and Nab incidences in Studies CT-P43 3.1 and 1.2 are not considered to be clinically significant and does not preclude the conclusion of no clinical meaningful differences between CT-P43 and US-Stelara, as the systemic exposure between the treatment groups are comparable.
Other (specify)	None

The clinical development for CT-P43 included three clinical studies which are listed below according to the order to which the studies were conducted:

- (1) Study CT-P43 1.1 (Failed PK similarity study): A 2-Part, randomized, double-blind, parallel-group, single-dose study to compare the pharmacokinetics, safety and immunogenicity of CT-P43, EU- Stelara, and US-licensed Stelara in healthy male subjects.

- (2) Study CT-P43 3.1 (Comparative clinical study): A double-blind, randomized, active controlled, parallel group study to compare efficacy and safety of CT-P43 and EU-Stelara in subjects with moderate to severe plaque psoriasis.
- (3) Study CT-P43 1.2 (PK similarity study): A randomized, double-blind, 3-arm, parallel group, single dose PK and safety of CT-P43, EU-Stelara and US-Stelara in healthy Japanese male subjects.

The clinical pharmacology review for this BLA primarily focused on the PK similarity study (Study CT-P43 1.2) and additional PK and immunogenicity data from the comparative clinical study (Study CT-P43 3.1) as these studies provided primary supportive evidence for demonstration of the biosimilarity of CT-P43. A summary of study outcome from the first PK similarity study, Study CT-P43 1.1 will be provided in this review for completeness; however, this failed PK similarity study would have limited regulatory utility. Study CT-P43 1.1 was designed as a two part randomized, double-blind, three-arm, parallel-group, single-dose, active comparator, first-in-human study in healthy male subjects conducted in Canada. In part 2 of the Study CT-P43 1.1, PK similarity of the proposed biosimilar, CT-P43 was assessed compared to EU-Stelara and US-Stelara in a three-way parallel treatment design, where, the upper limits of the 90% confidence intervals (CIs) exceeded 125.00% for the AUC_{0-inf} comparison of CT-P43 to EU-Stelara and to US-Stelara. The applicant conducted a root cause analysis with the aim to identify reasons for the failure to demonstrate PK similarity in Study CT-P43 1.1 Part 2. During investigation of Study CT-P43 1.1 Part 2, it was found that the clinical batches of CT-P43 used in the study had a higher protein content compared to EU-Stelara and US-Stelara batches. The post-hoc statistical analysis was conducted after dose correction in order to adjust for protein content of clinical batches and it was observed that the upper bounds of the 90% CIs for AUC_{0-inf} were closer to 125% which supported that the protein content difference impacted the PK comparisons between CT-P43 and Stelara products. Subsequently, Study CT-P43 1.2 was conducted with revised inclusion criteria to enroll a more homogenous population, and an increased sample size considering %CV in historical data, and the Applicant used US and EU Stelara batches with a similar protein content compared to the proposed biosimilar, CT-P43. Refer to Clinical pharmacology appendix for details on Study CT-P43 1.1. The Applicant provided sufficient details of the study design differences between Study CT-P43 1.1 and Study CT-P43 1.2. Based on these justifications, FDA considers Study CT-P43 1.2 more appropriately designed to comparatively assess PK between the products.

In the PK similarity study, CT-P43 1.2, the 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) of CT-P43 to US-Stelara, CT-P43 to EU-Stelara, and EU-Stelara to US-Stelara were contained within the prespecified margin of 0.8 to 1.25 for AUC_{0-inf} , C_{max} and AUC_{last} (Table 6). The results of the PK similarity study demonstrated that PK similarity was established between CT-P43, US-Stelara and EU-Stelara. The PK similarity study also established the PK component of scientific bridge which supports the relevance of EU-Stelara in the comparative clinical study.

Table 6. Summary of statistical analyses for assessment of PK similarity (Study CT-P43 1.2)

	Geometric Least Square Mean (Geometric CV%)			Geometric Least Square Mean Ratio* (90% CI)		
Primary						
	CTP43 (N=109)	US Stelara (N=105)	EU Stelara (N=104)	CTP43 vs US Stelara	CTP43 vs EU Stelara	EU Stelara vs US Stelara
AUC _{0-inf} (µg.h/mL)	204.86 (30.68%)	204.317 (31.19%)	186.243 (37.65%)	100.27 (93.21- 107.87)	109.9 (102.23- 118.35)	91.15 (84.66 - 98.15)
Cmax (µg/mL)	5.56 (34.96%)	5.87 (34.65%)	5.38 (37.94%)	94.84 (87.71- 102.57)	103.26 (95.47- 111.69)	91.85 (84.84 - 99.44)
Secondary						
AUC _{0-t} (µg.h/mL)	194.76 (35.64%)	198.15 (30.56%)	180.75 (37.58%)	98.27 (91.10- 106.04)	107.75 (99.85- 116.26)	91.22 (84.46-98.51)

*Presented as percent.

Source: FDA analysis using ADPC.xpt from Study CT-P43 1.2

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

There are no residual uncertainties from the clinical pharmacology assessment.

5.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

In the PK similarity study in Japanese healthy subjects, Study CT-P43 1.2, following a single 45 mg SC injection of CT-P43, EU-Stelara, or US-Stelara, the 90% CIs for the GMRs of CT-P43 to EU-Stelara, CT-P43 to US-Stelara, and EU-Stelara to US-Stelara for the tested PK parameters (i.e., AUC_{0-inf}, C_{max} and AUC_{last}) were all within the prespecified margin of PK similarity of 80-125%. These pairwise comparisons met the pre-specified criteria for PK similarity between CT-P43, EU-Stelara, and US-Stelara; thus, the PK portion of the scientific bridge was established to support the relevance of the data generated using EU-Stelara as a comparator in the comparative clinical study (Study CT-P43 3.1).

The incidence of ADA and NAb formation in subjects treated with CT-P43 was numerically lower compared to those treated with US-Stelara or EU-Stelara in both PK similarity study and comparative clinical study. However, the numerical differences in the incidence of ADA and NAb among CT-P43 and US-Stelara and EU-Stelara treatment groups, while similarly affecting the PK parameters of each product to a small extent (i.e., reduced systemic exposure in ADA positive subjects), do not appear to have a significant impact on PK overall, as the systemic exposure between the treatment groups are comparable.

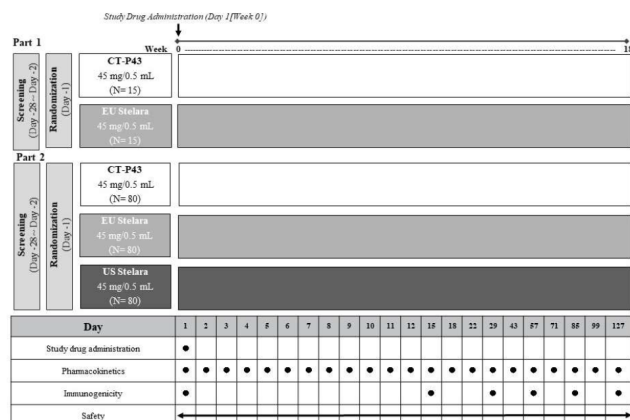
Overall, the submitted clinical pharmacology information supports a demonstration that there are no clinically meaningful differences between CT-P43 and US-Stelara.

5.3. Human Pharmacokinetic and Pharmacodynamic Studies

5.3.1. Clinical Pharmacology Study Design Features

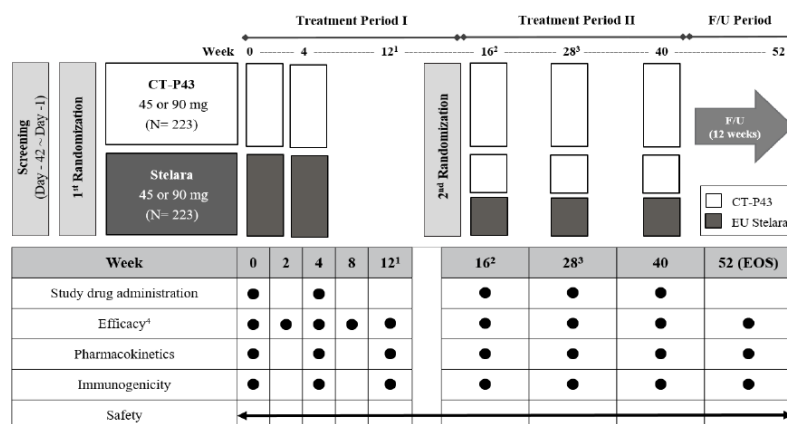
Three clinical studies provided PK data for this submission

- Study CT-P43 1.1: A 2-Part PK similarity study, randomized, double-blind, parallel-group, single-dose study to compare the pharmacokinetics, safety and immunogenicity of CT-P43, EU- Stelara, and US-licensed Stelara in healthy male subjects. The study design schema is shown in Figure 1.
- Study CT-P43 3.1: A double-blind, randomized, active controlled, parallel group comparative clinical study to compare efficacy and safety of CT-P43 and EU-Stelara in subjects with moderate to severe plaque psoriasis. The study design schema is shown in Figure 2.
- Study CT-P43 1.2: A PK similarity study, randomized, double-blind, 3-arm, parallel group, single dose PK and safety of CT-P43, EU-Stelara and US-Stelara in healthy Japanese male subjects. The study design schema is shown in Figure 3.

Figure 1. Study Schema for Study CT-P43 1.1

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

Source: BLA761338 Study CT-P43 1.1 Clinical Study Report⁶

Figure 2. Study Schema for Study CT-P43 3.1

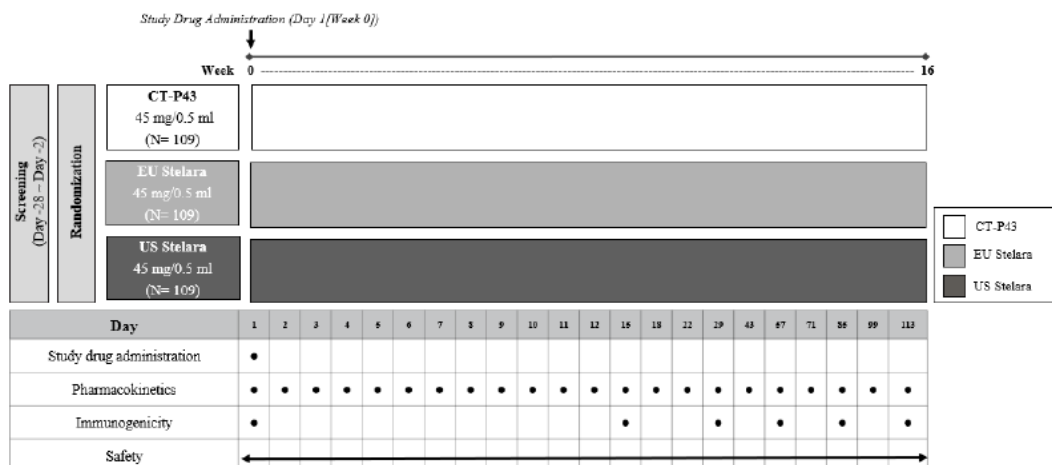
Source: BLA761338 Study CT-P43 3.1 Clinical Study Report⁷

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Figure 3. Study Schema for Study CT-P43 1.2

⁶ \\CDSESUB1\EVSPROD\bla761338\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\cltp4311\ct-p43-1-1-study-rpt-body.pdf

⁷ \\CDSESUB1\EVSPROD\bla761338\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5351-stud-rep-contr\cltp4331\ct-p4331-body.pdf



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

Source: BLA761338 Study CT-P43 1.2 Clinical Study Report⁸

5.3.2. Clinical Pharmacology Study Endpoints

Study CT-P43 1.1

In this PK similarity study, the primary endpoints were the PK parameters: AUC_{inf} and C_{max}. The secondary endpoints included determination of additional PK parameters such as, AUC_{last}, T_{max}, apparent volume of distribution (V_z/F), terminal elimination rate constant (λ_z) and incidence of ADAs. These endpoints are aligned with the FDA guidance for industry - Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (2016). FDA did not rely on this study to inform conclusions of PK similarity because of significant difference in protein content between CT-P43 and US-Stelara/EU Stelara products (Refer to Section 5.1 for additional details). Nonetheless, a summary of this study findings is provided in clinical pharmacology appendix in this review (Section 14.4) for completeness.

Study CT-P43 1.2

In this PK similarity study, the primary endpoints were the PK parameters: AUC_{inf} and C_{max}. The secondary endpoints included AUClast and incidence of ADAs. These endpoints are aligned with the FDA guidance for industry - *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (2016).

Study CT-P43 3.1

In this comparative clinical study, there were secondary, descriptive clinical pharmacology study endpoints like incidence of ADAs. While not identified as a study endpoint, a PK assessment was conducted by collecting sparse samples in this study. PK samples were collected at pre-specified time points and the descriptive statistics of mean serum concentrations of study drug were presented in the clinical study report.

⁸ [\\CDSESUB1\EVSPROD\bla761338\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\cltp4312\ct-p43-1-2-study-rpt-body.pdf](#)

5.3.3. Bioanalytical PK Method and Performance

A validated Electrochemiluminescence (ECL) Assay was used to quantify serum concentrations of study drug following SC administration of CT-P43, US-Stelara, and EU-Stelara in PK samples obtained from Studies CT-P43 1.2 and CT-P43 3.1.

The assay was adequately validated with sufficient precision and sensitivity. The in-study performance of the assay for sample analyses from Studies CT-P43 1.2 and CT-P43 3.1 was acceptable. Refer to 14.4.2 for detailed information about the assay validation and bioanalysis performance.

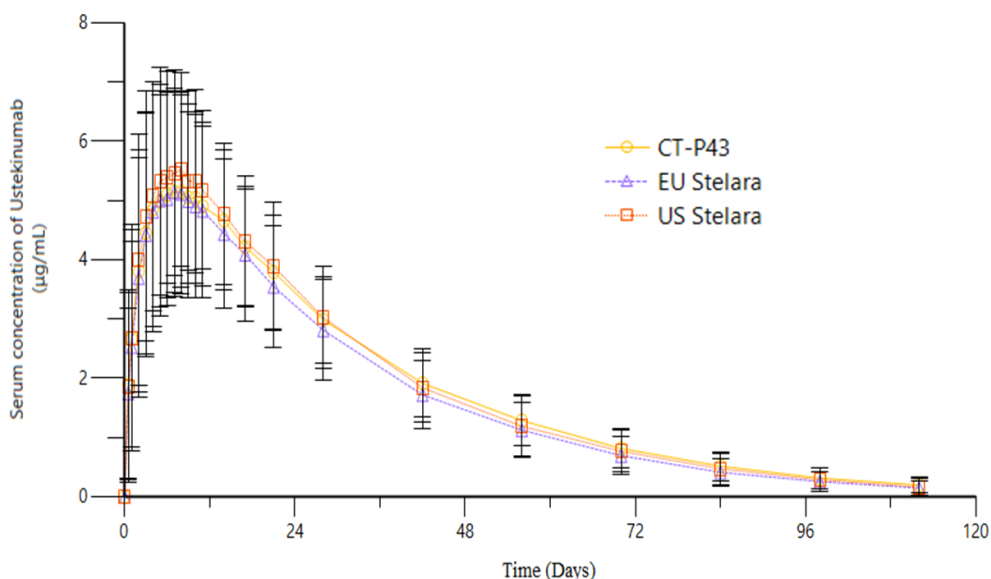
5.3.4. PK Similarity Assessment

Study CT-P43 1.2

PK similarity among CT-P43, US-Stelara and EU-Stelara has been demonstrated in a 3-arm, parallel PK similarity study in healthy Japanese subjects (Study CT-P43 1.2) in this study. PK samples were collected pre-dose on Day 1, and post-dose at 8 hr and 24 hr and on Days 3, 7, 9, 11, 13, 21, 28, 35, 49, 56, 70, 98 and 112. The point estimates and 90% CIs of the GMRs of PK parameters (AUC_{0-inf} , C_{max} and AUC_{last}) were all within the pre-defined criteria of 0.8 to 1.25 (Table 6). The mean serum concentration-time profiles were similar among CT-P43, US-Stelara and EU-Stelara treatment groups (Figure 4).

The PK parameters following a single 45 mg SC dose of CT-P43, US-Stelara and EU-Stelara are summarized in Table 7. In general, PK parameters and inter-subject variabilities were comparable across the three treatment groups. This study utilized EU Stelara and US Stelara batches with similar protein content compared to CT-P43. The protein content in CT-P43 batch 2NGP01 was 48.60 mg/syringe and the protein content for EU Stelara (batch: LJS3MMH) and US-Stelara drug products [batch: 21E141MF and LJS3MMA) was 49.29 mg/syringe.

Figure 4. Mean (+/- SD) Serum Concentration of Study Drug ($\mu\text{g/mL}$) in Study CT-P43 1.2



Source: FDA Analysis using ADPC.xpt from Study CT-P43 1.2

Table 7: Statistical Summary of PK Parameters of Study Drug by Treatment Arm in Study CT-P43 1.2

PK Parameters	Treatment groups		
	CT-P43 (N=110)	EU Stelara (N=104)	US Stelara (N=105)
	Geometric mean (GeoCV%)		
AUC _{inf} (µg*Day/mL)	204.87 (30.68%)	186.24 (37.66%)	204.32 (31.19%)
AUC _{0-last} (µg*Day/mL)	194.76 (35.65%)	180.75 (37.58%)	198.15 (30.57%)
C _{max} (µg/mL)	5.56 (34.96%)	5.39 (37.94%)	5.87 (34.66%)
t _{1/2} (h)	20.41 (23.83%)	18.62 (31.22%)	19.09 (24.86%)
T _{max} (h)	7.42 (49.72%)	7.32 (53.18%)	7.19 (51.25%)
V _{z/F} (mL)	6467 (28.72%)	6490.4 (33.88%)	6064.5 (29.03%)
MRT _{inf} (h)	33.3 (14.74%)	30.65 (25.25%)	31.24 (18.92%)
CL/F (mL/h)	219.65 (30.68%)	241.62 (37.66%)	220.25 (31.19%)

Source: FDA Analysis using ADPC.xpt from Study CT-P43 1.2

5.3.5. Inspection of PK Similarity Study

OSIS inspection: The primary PK similarity study, Study CT-P43 1.2 involved 6 study sites (5 clinical sites and 1 analytical site). An inspection request was sent to the Office of Study Integrity and Surveillance (OSIS). Refer to Sections 3.3 and 14 for details. No

objectionable condition was found to preclude approval of this biosimilar application.

5.3.6. PK of CT-P43 and EU-Stelara in Subjects with Psoriasis

Study CT-P43 3.1 is a comparative clinical efficacy and safety study comparing CT-P43 with EU-Stelara in subjects with moderate to severe chronic psoriasis. The study consisted of two treatment periods. In treatment period 1, the enrolled subjects were randomized to receive either 45 or 90 mg of CT-P43 or EU-Stelara by SC injection via PFS at Weeks 0, 4, 16 weeks based on subject's baseline body weight (45 mg for ≤ 100 kg vs. 90 mg for >100 kg). The primary clinical endpoint was improvement of baseline PASI score. Subjects who achieved at least 50% improvement from baseline in PASI (PASI 50) at Week 12 continue study drug administration in the Treatment Period 2 in all treatment groups. At Week 16, all subjects in the EU-Stelara group were randomly assigned again in a ratio of 1:1 to either continue EU-Stelara or undergo a transition to CT-P43. All subjects who were initially randomized to the CT-P43 group on Day 1 (Week 0) continued their treatment with CT-P43 until Week 40. Overall, the dosing schedule was as below:

- Week 0, Week 4, Week 16, Week 28 and Week 40 (Re-randomization was implemented at 16th week)

Serum concentrations of study drug were assessed at Weeks 0, 4, 12, 16, 28, 40, and 52 prior to study drug administration (except for Week 12 and EOS when the blood sample was taken at any time during that visit).

Serum concentrations were higher in CT-P43 compared to the EU-Stelara group from Week 4 through Week 16 (Table 8, Figure 5, Figure 6) in treatment period I. However, the serum concentrations were similar in treatment period 2 across the treatment groups of re-randomized subjects post Week 16 up to 40 weeks (Table 9, Figure 5, Figure 6). The comparable concentrations across treatment groups in the psoriasis subjects in treatment period 2, together with the results of the PK similarity study (Study CT-P43 1.2) supports a demonstration that there is no meaningful difference between CT-P43 and EU-Stelara.

Table 8. Serum Concentration ($\mu\text{g/mL}$) in Treatment period 1 in Study CT-P43 3.1

Visits	Treatment groups			
	CT-P43 (N=256) Mean $\pm$ SD (N, Min-Max) (Unit: $\mu\text{g/mL}$)		EU Stelara (N=248) Mean $\pm$ SD (N, Min-Max) (Unit: $\mu\text{g/mL}$)	
	45 mg	90 mg	45 mg	90 mg
Week 0	0	0	0	0

Week 4	2.41 ± 0.81 (196; 0.54-4.99)	3.39± 1.23 (58; 0.48-5.98)	2.22 ±0.87 (193; 0.23-5.18)	2.69 ±1.16 (53; 0.59-5.58)
Week 12	1.40± 0.63 (198; 0-3.45)	1.82±0.78 (58;0-4.09)	1.16 ±0.74 (192; 0-4.09)	1.35±0.79 (54;0-3.20)
Week 16	0.56±0.32 (195; 0-1.54)	0.66 ±0.34 (58;0-1.78)	0.45±0.37 (192; 0-1.71)	0.49±0.39 (54;0-1.93)

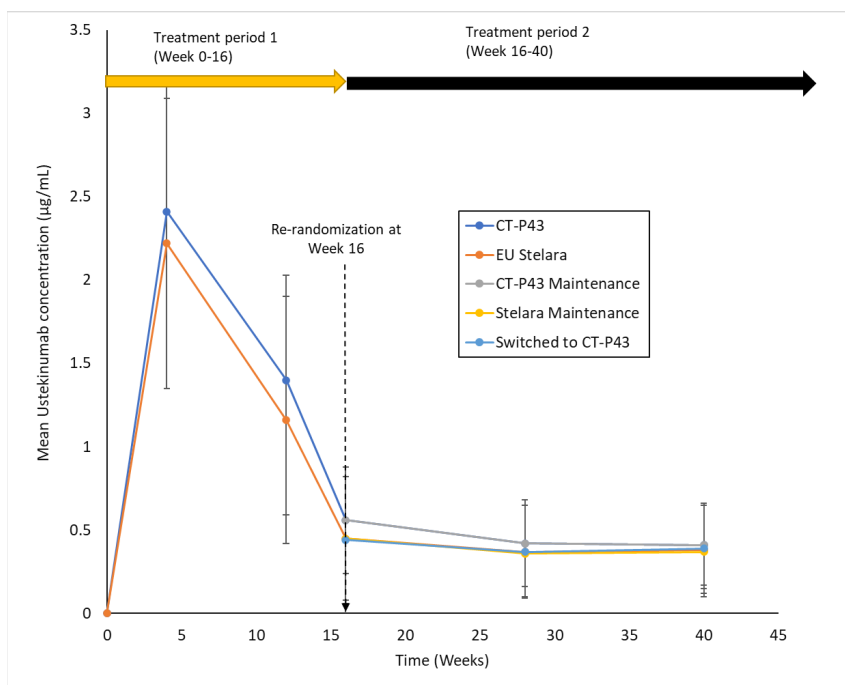
Source: FDA Analysis using ADPC.xpt from Study CT-P43 3.1

Table 9: Serum Concentration (µg/mL) in Treatment period 2 in Study CT-P43 3.1

Dose level	Visits	Treatment groups		
		CT-P43 Maintenance	EU - Stelara Maintenance	EU - Stelara Switched to CT-P43
		Mean±SD(N; Range) Unit: µg/mL		
45 mg	Week 16	0.56±0.32 (194; 0-1.55)	0.45±0.36 (97;0-1.53)	0.44±0.38 (97; 0-1.71)
	Week 28	0.42±0.26 (192;0-1.13)	0.36±0.29 (97; 0-1.62)	0.37±0.28 (97;0-1.24)
	Week 40	0.41±0.24 (189; 0-1.31)	0.37±0.29 (97;0-1.42)	0.39±0.27 (96; 0-1.25)
90 mg	Week 16	0.65±0.35 (59; 0-1.78)	0.51±0.43 (27; 0-1.94)	0.47±0.36 (27; 0-1.33)
	Week 28	0.49±0.31 (59; 0-1.45)	0.41±0.35 (27; 0-1.39)	0.43±0.33 (27; 0-1.74)
	Week 40	0.47±0.28 (57; 0-1.63)	0.49±0.31 (27; 0-1.12)	0.44±0.33 (27; 0-1.56)

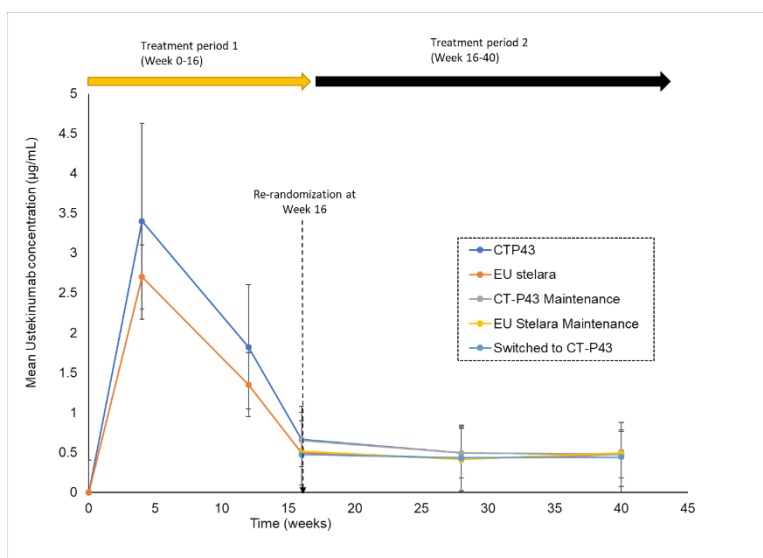
Source: FDA Analysis using ADPC.xpt from Study CT-P43 3.1

Figure 5. Mean (+/- SD) Serum Concentration of Study Drug (µg/mL) up to EOS (Linear Scale) in Study CT-P43 3.1 (PK Set, PK-Treatment Period II Subset): Dose: 45 mg



Source: FDA Analysis using ADPC.xpt from Study CT-P43 3.1

Figure 6. Mean (+/- SD) Serum Concentration of Study Drug (µg/mL) up to EOS (Linear Scale) in Study CT-P43 3.1 (PK Set, PK-Treatment Period II Subset): Dose: 90 mg



Source: FDA Analysis using ADPC.xpt from Study CT-P43 3.1

5.4. Immunogenicity Studies

Immunogenicity was assessed in both studies supporting this application:

(1) Study CT-P43 1.2

(2) Study CT-P43 3.1

5.4.1. Design features of the clinical immunogenicity assessment

The main objective for evaluation of the immunogenicity potential of CT-P43 was to address the immune response, by monitoring the formation of anti-drug antibody (ADA), including NAb and relate these to relevant clinical endpoints in clinical studies that have adequate sensitivity to detect an impact on PK, efficacy and safety (e.g., potentially immune-mediated adverse events [AEs]). Immunogenicity was assessed in healthy subjects following a single 45 mg SC dose of CT-P43, US-Stelara or EU-Stelara in Study CT-P43 1.2. Further, immunogenicity in psoriasis subjects was assessed following multiple SC doses of CT-P43 and EU-Stelara in Study CT-P43 3.1. The following section provides a high-level summary of the immunogenicity assessment. See Figure 2 and Figure 3 for more details regarding the study designs.

5.4.2. Immunogenicity endpoints

Blood samples collected for immunogenicity assessment were first tested for ADA. Samples that tested positive for ADA were further tested for Nab.

5.4.3. Immunogenicity assay's capability of detecting the ADA and NAb in the presence of proposed product, U.S.-licensed reference product, and non-U.S.-licensed comparator product (as applicable) in the study samples

The Applicant developed binding and neutralizing antibody assays that are suitable for detecting ADA and NAb in the presence of expected levels of CT-P43, US-Stelara and EU-Stelara. Refer to the OPQ Immunogenicity assay review for more details.

The immunogenicity data provided by Celltrion using the validated ADA and NAb assays discussed in the submission, indicate that both sets of assays are suitable for intended purpose as they are able to detect and confirm high rates of ADA and NAb+ samples for clinical studies (CT-P43 1.2 and CT-P43 3.1). It should be noted that the immunogenicity results from study CT-P43 1.1 were not considered for the purpose of biosimilarity.

5.4.4. Adequacy of the sampling plan to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA/NAb formation

The sampling plans were adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA/NAb formation.

- Study CT-P43 1.2: Samples for immunogenicity assessment were collected

predose on Day 1 (pre-dose), Day 15, Day 29, Day 57, Day 85, Day 113.

- Study CT-P43 3.1: Samples for immunogenicity assessment were collected at following time points:
 - Treatment Period 1: Week 0 (Day 1), Week 4 (Day 29), Week 12 (Day 85)
 - Treatment Period 2: Week 16 (Day 113), Week 28 (Day 197), Week 40 (Day 281) End-of-Study (EOS): Week 52 (Day 365)

5.4.5. Incidence of ADA and NAb

In healthy subjects following a single SC dose of 45 mg (Study CT-P43 1.2)

The immunogenicity of CT-P43 was numerically lower compared to those of US-Stelara and EU-Stelara in healthy adult subjects following a single 45 mg SC dose. The incidence of ADA and NAb by treatment group in Study CT-P43 1.2 is summarized in Table 10. The differences were not considered to be clinically significant.

Table 10: Immunogenicity Results in Study CT-P43 1.2 (Safety Set)

Treatment group	N	Anti-Drug antibody (ADA) response rate		NAb
		Baseline	Treatment-Induced	
CT-P43	111	4/111 (1.3%)	18/111 (16.2%)	14/111 (12.6%)
EU-Stelara	108	0	48/108 (44.4%)	18/108 (16.7%)
US-Stelara	106	0	42/106 (39.6%)	16/106 (15.1%)

Source: Clinical study report of Study CT-P43 1.2 (Adopted from Post text Table 14.3.5.7 Summary of Immunogenicity Results)

In study CT-P43 3.1, the immunogenicity results in both dose groups (45 mg and 90 mg) indicate that CT-P43 appears to be less immunogenic. In the 45 mg dose group, 21 (10.7%) and 42 (21.1%) subjects in the CT-P43 and EU-Stelara groups, respectively, were found to have at least one ADA positive result after exposure to the study drug up to week 16 (Table 11). In 90 mg group, 5 (8.5%) and 19 (35.2%) subjects in the CT-P43 and EU-Stelara groups, respectively, exhibited at least one ADA positive result after exposure to the study drug at end of treatment period I (prior to re-randomization to start switching treatment) (Table 12).

After week 16 in treatment period II, subjects in EU-Stelara group were re-randomized to EU Stelara maintenance and Switching treatment group where the subject received CT-P43. At the end of treatment period II, in 45 mg dose group, the ADA response rate in EU-Stelara maintenance and Switching arm were 33.7% and 30.9%, respectively (Table 11). In contrast to 45 mg group, a numerical slight increase in ADA response rate was observed in switching arm in 90 mg group. At the end of treatment period II, in 90 mg dose group, the ADA response rate in EU-Stelara maintenance and Switching arm were 37% and 44.4%, respectively (Table 12).

Table 11: Frequency of ADA and NAb by Dose (45 mg) in Study CT-P43 3.1 (Safety Set)

Parameters	Treatment Period I (From 0 – Week 16, pre-dose)		Treatment period II (From Week 16, post dose to End of Study)		
	CT-P43 (N=197)	EU- Stelara (N=199)	CT-P43 Maintenance (N=194)	EU-Stelara Maintenance (N=98)	Switched to CT-P43 (N=97)
% of Subjects showing at least one positive ADA results	21 (10.7%)	42 (21.1%)	25 (12.9%)	33 (33.7%)	30 (30.9%)
% of subjects showing at least one positive Nab result	12 (6.1%)	20 (10.6)	14 (7.2%)	17 (17.3%)	14 (14.4%)

Source: BLA761338; Responses to request for information received via email on 11 March 2024⁹

Table 12: Frequency of ADA and NAb by Dose (90 mg) in Study CT-P43 3.1 (Safety Set)

Parameters	Treatment Period I (From 0 – Week 16, pre-dose)		Treatment period II (From Week 16, post dose to End of Study)		
	CT- P43 (N=59)	EU- Stelara (N=54)	CT-P43 Maintenance (N=59)	EU-Stelara Maintenance (N=27)	Switched to CT-P43 (N=27)

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% of Subjects showing at least one positive ADA results	5 (8.5%)	19 (35.2%)	8 (13.6%)	10 (37.0%)	12 (44.4%)
% of subjects showing at least one positive Nab result	3 (5.1%)	11 (20.4%)	6 (10.2%)	5 (18.5%)	9 (33.3%)

Source: BLA761338; Responses to request for information received via email on 11 March 2024¹⁰

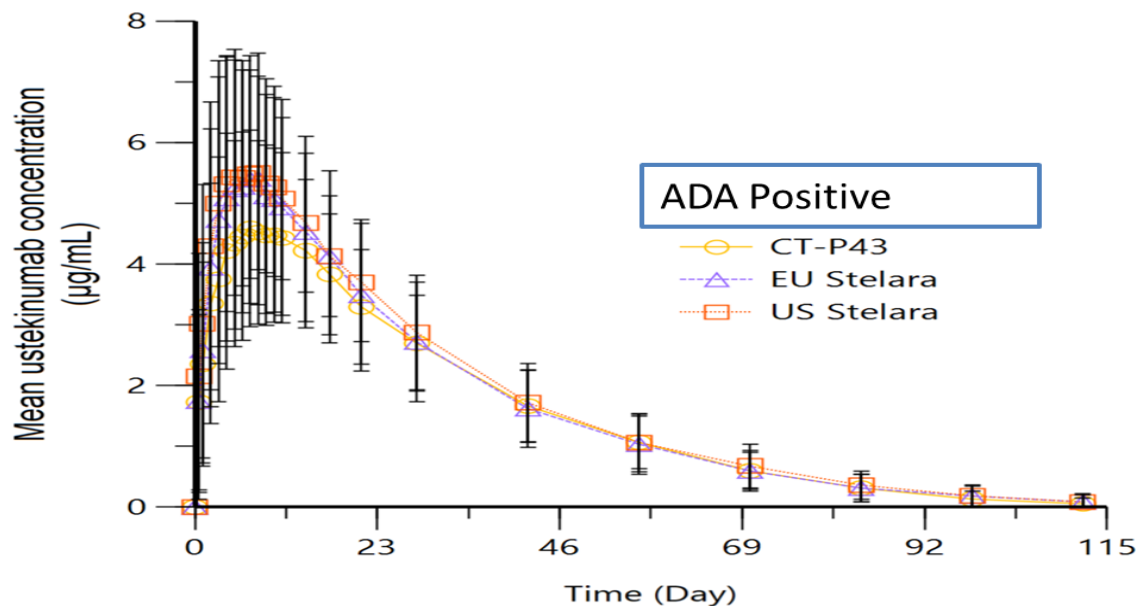
Impact of ADA on the PK, safety, and clinical outcomes of the proposed product

Impact of ADA on PK

In healthy subjects, in the PK similarity study CTP-P43 1.2, the development of ADAs resulted in decrease in AUC_{inf} in each treatment group. The development of ADAs increased the clearance and decreased the half-lives of each study drug, (CT-P43, US-Stelara and EU-Stelara). Similarly, in the multiple dose comparative clinical study in subjects with plaque psoriasis, the development of ADAs resulted in a decrease in trough concentrations in both CT-P43 and EU-Stelara at each study visit through Week 28 (Table 15).

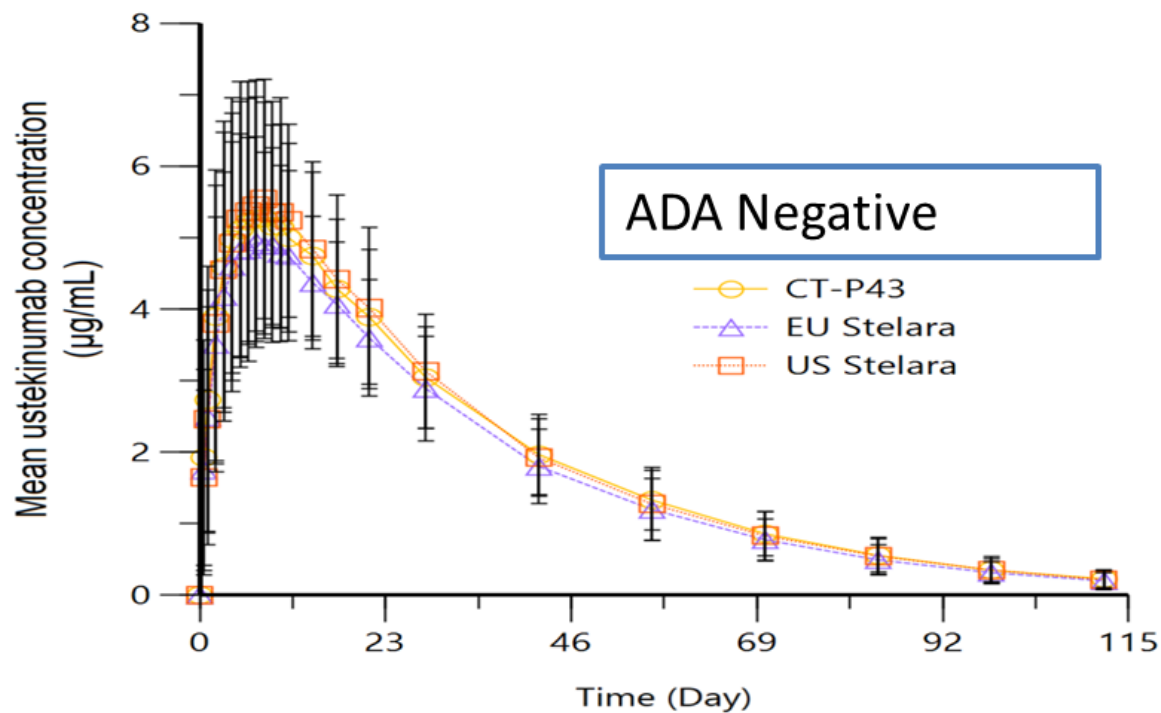
Figure 7. Mean serum concentration of study drug in ADA positive subjects in Study CT-P43 1.2

¹⁰ \\CDSESUB1\EVSPROD\bla761338\0018\m1\us\clinical-information-amendment-1.pdf



Source: FDA Analysis using data from ADPC.xpt file of Study CT-P43 1.2

Figure 8. Mean serum concentration of study drug in ADA negative subjects in Study CT-P43 1.2



Source: FDA Analysis using data from ADPC.xpt file of Study CT-P43 1.2

Table 13: Percent Change in C_{max} and AUC_{inf} by ADA Status (Study CT-P43 1.2)

Treatment arm	Exposure PK parameters	ADA Status (N)	Geometric Mean (CV%)	Change ^a in ADA positive group%
CT-P43	AUC _{inf} (µg.day/mL)	Negative (N=91)	212.88 (27.56)	Decreased by 20.72%
		Positive (N=18)	168.76 (38.21)	
	C _{max} (µg/mL)	Negative (N=92)	5.73 (33.98)	Decreased by 9.54%
		Positive (N=18)	4.77 (36.40)	
EU Stelara	AUC _{inf} (µg.day/mL)	Negative (N=57)	194.88 (29.76)	Decreased by 10.58%
		Positive (N=47)	176.28 (45.48)	
	C _{max} (µg/mL)	Negative (N=57)	5.27 (34.59)	Increase by 5.12%
		Positive (N=47)	5.54 (41.96)	
US Stelara	AUC _{inf} (µg.day/mL)	Negative (N=63)	213.66	Decreased by 5.06%
		Positive (N=42)	191.06	
	C _{max} (µg/mL)	Negative (N=63)	5.81 (33.91)	Increased by 2.5%
		Positive (N=42)	5.95 (36.13)	

^a Calculated as (Geometric mean in positive ADA subgroup – Geometric mean in negative ADA subgroup)/ Geometric mean in ADA negative subgroup expressed in percentage (%)

Source: FDA Analysis using data from CSR of CT-P43 1.2 (ADPC.xpt file)

Table 14: Percent Change in Clearance and half-life by ADA Status (Study CT-P43 1.2)

PK Parameters	Treatment arm	ADA Status (N)	Geo Mean (CV%)	Change in ADA positive group ^a
CL/F (mL/h)	CT-P43	Negative (N=91)	211.39 (27.56)	Increased by 26%
		Positive (N=18)	266.65 (38.21)	
	EU Stelara	Negative (N=57)	230.91 (29.76)	Increased by 11%
		Positive (N=47)	255.27 (45.48)	
	US Stelara	Negative (N=63)	210.61 (29.21)	Increased by 12%
		Positive (N=42)	235.53 (33.11)	
t _{1/2} (day)	CT-P43	Negative (N=91)	21.48 (18.96)	Decreased by 27%
		Positive (N=18)	15.77 (28.83)	
	EU Stelara	Negative (N=57)	20.65 (18.76)	Decreased by 21%
		Positive (N=47)	16.42 (38.26)	
	US Stelara	Negative (N=63)	20.38 (21.73)	Decreased by 15%
		Positive (N=42)	17.29 (26.06)	

^a Calculated as (Geometric mean in positive ADA subgroup – Geometric mean in negative ADA subgroup)/ Geometric mean in ADA negative subgroup

Source: FDA Analysis using ADPC.xpt data from CT-P43 1.2 study

Similarly as the PK similarity study CT-P43 1.2, in Study CT-P43 3.1, following the multiple dose in subjects with plaque psoriasis, the development of ADAs resulted in a slight numerical decrease in trough concentrations in both CT-P43 and EU-Stelara at each study visit through Week 16 (treatment period 1, Table 15).

Table 15: Serum Concentrations of Study Drug (µg/mL) by ADA Status in Study CT-P43 3.1 (treatment period 1)

Treatment arm	Time points	ADA Status (N)	Mean Trough Concentration (SD) Unit: µg/mL
45 mg dose group			
CT-P43	Week 4 (Pre-dose)	Negative (N=172)	2.4 (0.8)
		Positive (N=24)	2.3 (0.9)
	Week 12	Negative (N=174)	1.4 (0.6)
		Positive (N=24)	1.1 (0.7)
	Week 16 (Pre-dose)	Negative (N=174)	0.6 (0.3)
		Positive (N=24)	0.3 (0.3)
EU Stelara	Week 4 (Pre-dose)	Negative (N=140)	2.3 (0.8)
		Positive (N=53)	2.0 (0.9)
	Week 12	Negative (N=138)	1.3 (0.7)
		Positive (N=54)	0.8 (0.6)
	Week 16 (Pre-dose)	Negative (N=139)	0.5 (0.4)
		Positive (N=53)	0.3 (0.3)
90 mg dose group			
CT-P43	Week 4 (Pre-dose)	Negative (N=53)	3.5 (1.1)
		Positive (N=5)	2.0 (1.6)
	Week 12	Negative (N=53)	1.9 (0.7)
		Positive (N=5)	0.8 (0.8)
	Week 16 (Pre-dose)	Negative (N=53)	0.7 (0.3)
		Positive (N=5)	0.2 (0.3)
EU Stelara	Week 4 (Pre-dose)	Negative (N=33)	2.8 (1.1)
		Positive (N=20)	2.5 (1.3)
	Week 12	Negative (N=34)	1.4 (0.7)
		Positive (N=20)	1.2 (0.9)
	Week 16	Negative (N=34)	0.6 (0.4)
		Positive (N=20)	0.4 (0.4)

Source: CSR of Study CT-P43 3.1 study

Impact of ADA on Safety

Overall, no apparent impact of ADA on safety of CT-P43, US-Stelara, or EU-Stelara was observed in the PK similarity study (CT-P43 1.2) and clinical similarity study (CT-P43 3.1). Cases of injection site reactions were reported in all three treatment groups. In general, the number of injection site injuries were slightly higher in the CT-P43 treatment group compared to the EU-Stelara and US Stelara treated groups. There were no meaningful differences seen in other immunogenic safety events (i.e. anaphylaxis, cytokine release syndrome) among the 3 treatment arms. Refer to *Section 6.4: Clinical conclusion on immunogenicity* for information on impact of ADA response on safety.

Table 16: Summary of TEAEs in PK similarity study CT-P43 1.2 by ADA status

Number of Subjects (%) with at Least 1 Adverse Event	Data collected from overall safety monitoring period (upto 20 weeks post dose)					
	CT-P43 (N = 18)		EU-Stelara (N = 48)		US-Stelara (N = 42)	
ADA Status	ADA Positive	ADA Negative	ADA Positive	ADA Negative	ADA Positive	ADA Negative
TEAE	10 (55.6)	50 (54.3)	26 (54.2)	28 (46.7)	24 (57.1)	24 (37.5)
TESAE	0	0	0	0	0	0
Injection Site Reaction	2 (11.1)	19 (20.7)	4 (8.3)	10 (16.7)	4 (9.5)	6 (9.4)
Hypersensitivity reaction	0	0	1 (2.1)	0	0	0

Source: Final CSR Study CT-P43 1.2 Post-text Table 14.3.1.1.a and 14.3.1.1.b

In Study CT-P43 3.1, 2 Injection Site reaction (ISR)s occurred in the ADA positive subgroup of CT-P43 treatment group and 1 ISR occurred in the ADA positive subgroup of EU-Stelara treatment group (Table 17). One subject in the ADA positive subgroup of the CT-P43 treatment arm experienced hypersensitivity reaction. Injection Site reactions were generally comparable between the treatment groups. There is no meaningful differences in safety profile based on ADA status. Refer to *Section 6.4: Clinical conclusion on immunogenicity* for additional information on impact of ADA response on safety.

Table 17: Summary of TEAEs in clinical efficacy study (CT-P43 3.1) by ADA status

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

Note: Percentages are calculated by using the number of subjects in each ADA subgroup as denominator
Source: Section 5.3.5.3 - Reports of Analyses of Data from More than One Study: CT-P43 Post-hoc analysis - Study 3.1; Table 4.23

Impact of ADA on Efficacy

The results of the primary efficacy endpoint (the mean percent improvement from baseline in Psoriasis Area and Severity Index [PASI] score at Week 12) per ADA Status are summarized in Table 18. 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. Refer to *Section 6.4: Clinical conclusion on immunogenicity* in this review document for additional information on impact of ADA response on efficacy endpoint.

Table 18: Summary of Percent Improvement from Baseline in PASI Score at Week 12 by ADA Status at Week 12 in Study CT-P43 3.1

Statistic	CT-P43		EU-Stelara	
	ADA positive at Week 12	ADA negative at Week 12	ADA positive at Week 12	ADA negative at Week 12
n	21	235	57	191
Mean	84.86	86.16	80.39	85.06
SD	20.499	14.273	21.245	16.103
Minimum	5.4	38.4	0.0	24.4
Median	91.04	90.15	88.57	91.62
Maximum	100.0	100.0	100.0	100.0

Source: Final CSR Study CT-P43 3.1 Post-text Table 14.2.1.1a

In summary, the immunogenicity of CT-P43 was evaluated in healthy male subjects in CT-P43 1.2 and plaque psoriasis subjects in Study CT-P43 3.1. Numerical differences in the incidence of ADA and NAb between CT-P43 and US-Stelara and EU-Stelara were observed. However, the PK parameters of each product are similarly affected by

ADA to a small extent (i.e., reduced systemic exposure) and the overall exposure between the three products was comparable. Further, there did not appear to be any impact on safety or efficacy based on ADA status. Therefore, these numerical differences in the incidence of ADA and NAb between CT-P43 and US-Stelara and EU-Stelara do not appear to be clinically significant.

Clinical Pharmacology review concludes that PK similarity between CT-P43, EU-Stelara and US-Stelara was established in study CT-P43 1.2 and the use of EU-Stelara in the comparative clinical study, CT-P43 3.1 is supported by the results of the PK similarity study.

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6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

Comparative Efficacy: The comparative efficacy of CT-P43 and EU-Stelara was evaluated in Study CT-P43 3.1, a double-blind, randomized, multi-center, parallel-group, efficacy and safety study in subjects with moderate to severe plaque psoriasis (PsO) during 40 weeks of treatment. Comparative efficacy were assessed for primary endpoint, the mean percent improvement in PASI at Week 12. The 90% confidence interval (CI) for the treatment difference based on the mean percent change from baseline in PASI at Week 12 for the Modified Intent-to-Treat (mITT) Analysis Set, the supportive per- protocol (PP) Analysis Set, as well as sensitivity analyses, all fall within the similarity margins of ± 10 [mITT: (-0.23, 4.32), PP: (-0.29, 4.29)]. Thus, the study showed no meaningful differences between the CT-P43 and EU-Stelara treatment arms regarding the primary efficacy endpoint. In addition, secondary efficacy endpoints demonstrated no meaningful differences between the CT-P43 and EU-Stelara treatment arms.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties from the statistical perspective.

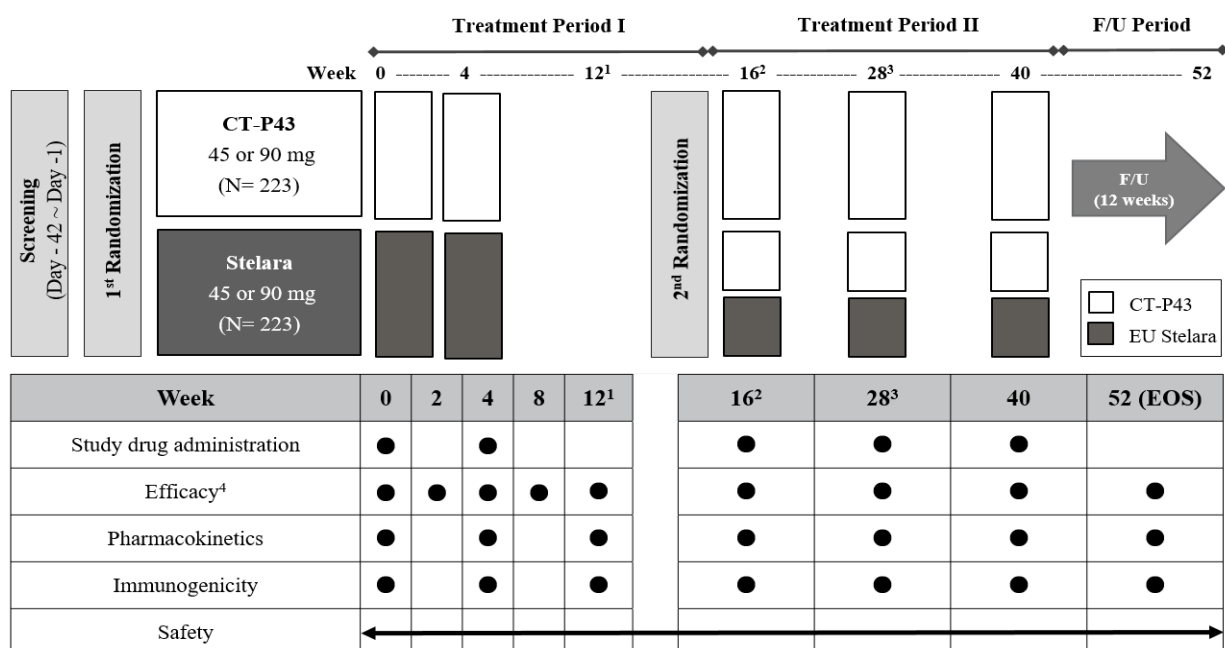
6.2. Review of Comparative Clinical Studies with Statistical Endpoints

6.2.1. STUDY CT-P43 3.1

Data and Analysis Quality

There are no concerns regarding data quality and integrity for Study CT-P43 3.1. Refer to Sections 3.4 and 8 for more detailed discussion supporting this conclusion.

Study Design and Endpoints



Abbreviations: EOS, end-of-study; N, number of subjects; PASI, Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment. F/U: follow-up

¹ At Week 12, it was recommended that subjects who achieved at least PASI 50 continue study drug administration in Treatment Period II in all groups.

² Prior to dosing at Week 16, all subjects underwent the second randomization process. Subjects who were initially randomly assigned to EU-Stelara were randomly assigned again in a ratio of 1:1 to either continue EU-Stelara or undergo transition to CT-P43. All subjects who were initially randomly assigned to the CT-P43 group on Day 1 (Week 0) continued their treatment with CT-P43 until Week 40.

³ At Week 28, it was recommended that subjects who achieved at least PASI 75 continue further study drug administration in all groups.

⁴ The investigator-reported outcomes assessments (i.e., PASI, sPGA) were performed by a qualified efficacy assessor at the site. If possible, it was recommended that the same assessor perform the investigator-reported outcomes assessments throughout the entire study period.

Source: Figure 9-1 in the Applicant's Clinical Study Report

Study CT-P43 3.1 was a randomized, active-controlled, double-blind, multicenter, Phase 3 study designed to evaluate efficacy, PK, QoL and overall safety including immunogenicity of CT-P43 compared with EU-Stelara administered by subcutaneous (SC) injection via pre-filled syringe (PFS) in subjects with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

The duration of the study was to be up to 58 weeks, which included Screening (up to 6 weeks), Treatment Period I and II (up to 40 weeks), and off-dose follow-up period (12 weeks) prior to the End-of-Study (EOS) visit.

On Day 1 (Week 0), subjects who met all the inclusion criteria and none of the exclusion criteria were enrolled in the study and randomly assigned in 1:1 ratio (the first randomization) to receive either CT-P43 or EU-Stelara by SC injection. In particular, they 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 subject's baseline body weight. Treatment assignment was stratified by the following: country, body weight (≤ 100 kg vs. > 100 kg), prior biological use approved for psoriasis treatment (Yes or No).

The second dose was given at Week 4. It was recommended that subjects who achieved PASI 50 at Week 12 continue study drug administration in the Treatment Period II in all groups.

Prior to the third dosing at Week 16 in Treatment Period II, all subjects in the EU-Stelara treatment group underwent the second randomization process. Subjects who were initially randomly assigned to EU-Stelara were randomized again in a ratio of 1:1 to either continue EU-Stelara or transition to CT-P43. All subjects who were initially randomly assigned to CT-P43 at Day 2 will continue their treatment with CT-P43 until Week 40. The second randomization of the EU-Stelara treatment group was stratified by dose at Week 16 (45 mg vs. 90 mg).

The fourth dose was administered at Week 28. It was recommended that all subjects who achieved PASI 75 at Week 28 received the fifth dose at Week 40. An End-of-Study visit was at Week 52 for all subjects who either completed or discontinued study drugs.

The study screened 574 subjects, and 65 subjects had screening failure. Thus, it enrolled and randomized 509 subjects, from 34 study centers in 4 countries: Estonia, Korea, Poland, and Ukraine.

The primary efficacy endpoint is the mean percent improvement from baseline in PASI score at Week 12.

The secondary efficacy endpoints are:

- 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 subjects 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
- The proportion of subjects 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
- The change in Dermatology Life Quality Index (DLQI) score from baseline at Weeks 2, 4, 8, 12, 16, 28, 40, and 52

Statistical Methodologies

Analysis Populations

For the primary efficacy endpoint, the primary efficacy analysis and sensitivity analysis on primary efficacy endpoint was conducted on the Modified ITT (mITT) Set, and a support analysis was conducted on the Per-Protocol Set (PPS). All analyses for the secondary efficacy endpoints were conducted on the mITT Set, PPS, and mITT – Treatment Period II Subset. The definition of each analysis set is described as follows.

ITT Set: Defined as all subjects who were randomly assigned to receive study drug (CT-P43 or EU-Stelara).

Modified ITT (mITT) Set: Defined as all subjects who were randomly assigned and received at least 1 dose (full or partial) of study drug (CT-P43 or EU-Stelara).

Per-Protocol Set (PPS): Defined as all randomly assigned subjects who received the full dose of study drug (CT-P43 or EU-Stelara) at Weeks 0 and 4 and had a PASI assessment at baseline and Week 12. The subjects who had any major protocol deviation which affected the interpretation of study results of primary efficacy endpoint were excluded from PPS.

mITT-Treatment Period II: Defined as all subjects in mITT set who are randomly assigned at Week 16 prior to dosing and received at least 1 dose (full or partial) of study drug (CT-P43 or EU-Stelara) at or after Week 16.

Efficacy Evaluation

Primary Efficacy Endpoint

The primary efficacy endpoint, the percent improvement from baseline in PASI score at Week 12 was defined as:

$$\frac{PASI\ Score\ at\ Baseline - PASI\ Score\ at\ Week\ 12}{PASI\ Score\ at\ Baseline} \times 100$$

Primary Efficacy Analysis

For the primary efficacy endpoint, the primary efficacy analysis was conducted on the mITT Set using an analysis of covariance (ANCOVA) model coupled with multiple

imputation (MI) with the missing at random (MAR) assumption for missing data handling. The ANCOVA model included 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 using the same ANCOVA model on the PPS.

Handling of Missing Data

Multiple imputation with the MAR assumption was applied 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 subjects with baseline PASI score in mITT Set was 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 is 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 comparison of efficacy, if the 90% CI for the treatment difference in the mean percent improvement in PASI between the CT-P43 and EU-Stelara falls entirely within the specified margins of $\pm 10\%$, we conclude that there are no meaningful differences between the two products with respect to efficacy.

Statistical Reviewer's Comment:

When the applicant generated the multiple imputed datasets, they only included the baseline covariates in the model to impute the missing PASI values at Week 12, rather than including their historical non-missing PASI values in the previous weeks as well in the model. The latter approach will produce more accurate imputation than the former approach. However, considering that there are only 5 subjects in this study with missing data and the study result is robust, use of either imputation approach results in the same conclusion.

Sensitivity Analysis

In order to evaluate the impact of missing data on the primary efficacy endpoint results, additional analyses with missing data imputation were conducted for the primary efficacy endpoint of PASI at Week 12 in the mITT Set.

- Tipping Point Analysis

To assess the robustness, a sensitivity analysis using tipping point analysis under missing not at random (MNAR) scenario was conducted for the primary efficacy

endpoint in the mITT Set. In the tipping point analysis, imputed values were shifted gradually from the imputed values by MI under MAR by treatment groups (CT-P43 vs. EU-Stelara) to make MNAR scenarios. A point estimate and 90% CI for treatment difference were 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.

- 'Best-Worst Case' and 'Worst-Best Case' Analysis

Two sensitivity analyses with 'best-worst case' scenario and 'worst-best case' scenario were conducted to assess the robustness. 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 90% 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.

Key Secondary Efficacy Analysis

- PASI Score

PASI score was summarized using descriptive statistics of actual value by treatment group at each scheduled visit. The mean percent improvement from baseline in PASI score was summarized by treatment group at specified visit. The difference on means between CT-P43 and EU-Stelara and its 95% CI in PASI score and the mean percent improvement from baseline in PASI score were estimated using t-test at specified visit.

- Proportions of PASI 50/75/90/100 responders

The number and proportion of subjects who achieved at least 50/75/90/100% improvement from baseline in PASI (PASI 50/75/90/100) were summarized by treatment group at each scheduled visit. The difference between CT-P43 and EU-Stelara and its 95% CIs of the proportion of PASI 50/75/90/100 responders were estimated using Wald method at specified visits.

Statistical Reviewer's Comment:

For secondary efficacy endpoints in this study, the 95% CI of the treatment effect was reported for exploratory purpose. What this also means is that no multiplicity adjustment is considered for these analyses. This implies that there are no adjustments made for multiplicity in these analyses.

Subject Disposition

Table 19 shows the number of subjects in different analysis sets. There was no difference between ITT set and mITT set, both comprised of 509 subjects including 256 in CT-P43 and 253 in EU-Stelara. For simplicity, we use ITT set in this report. Out of the 509 ITT (mITT) subjects, 496 (97.4%) were included in the PPS (252 in CT-P43 and 244 in EU-Stelara). Major protocol deviations were reported for 6 (1.2%) subjects in total and were excluded from the PPS for the reason of prohibited medication or treatment which could affect Week 12 efficacy assessment (3 in CT-P43 and 3 in EU-Stelara).

There was no difference between the ITT-Treatment Period II set and mITT-Treatment Period II as well, both comprised of 253 subjects in CT-P43 Maintenance, 125 in EU-Stelara Maintenance, and 124 in Switched to CT-P43 treatment group. For simplicity, we use ITT-Treatment Period II set in this report

Table 19. Number of Subjects in Statistical Analysis Sets

	Treatment Period I		Treatment Period II		
	CT-P43	EU-Stelara	CT-P43 Maintenance	EU-Stelara Maintenance	Switched to CT-P43
ITT Set	256	253	N/A	N/A	N/A
mITT Set	256	253	N/A	N/A	N/A
ITT – Treatment Period II subset	N/A	N/A	253	125	124
mITT – Treatment Period II subset	N/A	N/A	253	125	124
PPS	252	244	N/A	N/A	N/A

Source: Table 2.7.3-1 in the Applicant's Clinical Study Report

Table 20 summarizes the subject disposition in Treatment Period I for the ITT Set (i.e., mITT set). A total of 509 subjects were screened, and 65 subjects had screen failure. The most frequently reported primary reason for screening failure was inclusion/exclusion criteria not met (49 subjects). A total of 509 subjects were enrolled and randomized into the study, with 256 subjects assigned to CT-P43 group and 253 subjects assigned to EU-Stelara group. All 509 subjects were included in the Intent-to-Treat (ITT) Analysis Set, and the mITT Analysis Set.

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

During Treatment Period I, a total of 7 subjects (1.4%) discontinued the study drug and terminated from the study prior to Week 16. The proportion of subjects with treatment or

study discontinuation before Week 16 was similar between the CT-P43 group and EU-Stelara group. The reported primary reasons for study drug discontinuation were withdrawal by subject (1.0%), lost to follow-up (0.2%) and investigator decision (0.2%). The reported primary reasons for study termination were withdrawal by subject (1.2%) and lost to follow-up (0.2%).

Table 20 **Summary of Subject Disposition (Treatment Period I): ITT Set**

	CT-P43 (N=256)	Stelara (N=253)	Total (N=509)
	Number (%) of patients		
Total number of patients			
Screened ¹	-	-	574
Screening failure	-	-	65
Primary reason for screening failure²			
Inclusion/Exclusion criteria not met	-	-	49
Patient withdrew consent	-	-	14
Other	-	-	2
Randomized (1st)	256	253	509
Administered the study drug in Treatment Period I	256 (100.0%)	253 (100.0%)	509 (100.0%)
Discontinued the study drug in Treatment Period I	3 (1.2%)	4 (1.6%)	7 (1.4%)
Terminated the study in Treatment Period I	3 (1.2%)	4 (1.6%)	7 (1.4%)
Primary reason for study drug discontinuation in Treatment Period I			
Lost to follow-up	0	1 (0.4%)	1 (0.2%)
Investigator decision	1 (0.4%)	0	1 (0.2%)
Withdrawal by patient	2 (0.8%)	3 (1.2%)	5 (1.0%)
Time on study drug prior to discontinuation in Treatment Period I (days)³			
n	3	4	7
Mean	19.7	15.5	17.3
SD	16.17	16.76	15.25
Minimum	1	1	1
Median	29.0	15.0	29.0
Maximum	29	31	31
Primary reason for study termination in Treatment Period I			
Withdrawal by patient	3 (1.2%)	3 (1.2%)	6 (1.2%)
Lost to follow-up	0	1 (0.4%)	1 (0.2%)

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

¹. Includes Screening failures.

². Includes Screening failures only.

3. Only for subjects 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).

Sources: Post-text Table 14.1.1 and Data Listings 16.2.1.1, and 16.2.2.3.

Source: Table 10-1 in the Applicant's Clinical Study Report

Table 21 summarized subject disposition for Treatment Period II. In Treatment Period II, 502 subjects were randomly assigned to receive study drug; There were 253, 125, and 124 subjects in the CT-P43 maintenance, EU-Stelara maintenance, and Switched to CT-P43 groups, respectively. After re-randomization at Week 16, among the 502 subjects, 15 (3.0%) subjects discontinued the study drug (10 (4.0%), 3 (2.4%), and 2 (1.6%) in the CT-P43 maintenance, EU-Stelara maintenance, and Switched to CT-P43 groups, respectively). The most common reason for study drug discontinuation after re-randomization was withdrawal by subject (overall 1.6%: 2.0%, 1.6%, and 0.8% in the CT-P43 maintenance, EU-Stelara maintenance, and Switched to CT-P43 groups, respectively).

Of the 502 subjects, 14 (2.8%) terminated from the study (10 (4.0%), 3 (2.4%), and 1 (0.8%) in the CT-P43 maintenance, EU-Stelara maintenance, and Switched to CT-P43 groups, respectively). The most common reason for study termination was also withdrawal by subject (overall 2.2%: 2.8%, 2.4%, and 0.8% in the CT-P43 maintenance, EU-Stelara maintenance, and Switched to CT-P43 groups, respectively).

A total of 483 (96.2%) subjects completed the study (239 (94.5%), 122 (97.6%), and 122 (98.4%) in the CT-P43 maintenance, EU-Stelara maintenance, and Switched to CT-P43 groups, respectively).

Table 21 Summary of Subject Disposition (Treatment Period II) ITT – Treatment Period II Subset

Treatment Period II	Number (%) of patients			
Randomized (2nd)	253	125	124	502
Administered the study drug	253 (100.0%)	125 (100.0%)	124 (100.0%)	502 (100.0%)
Discontinued the study drug	10 (4.0%)	3 (2.4%)	2 (1.6%)	15 (3.0%)
Terminated the study	10 (4.0%)	3 (2.4%)	1 (0.8%)	14 (2.8%)
Completed the study¹	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 subjects 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 subjects 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).

Sources: Post-text Table 14.1.1 and Data Listings 16.2.1.1, and 16.2.2.3.

Table 10-2 in Applicant's Study Report.

Demographics and Baseline Characteristics

Table 22 reports the demographic characteristics for the ITT Analysis Set. Overall, demographic characteristics were generally balanced and similar between the treatment groups in Study CT-P43 3.1. Among the 509 subjects, the mean age was 42.4 years. There were more male subjects (334 (65.6%)) than female subjects (175 (34.4%)). The majority of subjects were White (461 (90.6%) subjects), and the rest were Asian (48 (9.4%) subjects). The mean (SD) baseline BMI of subjects was 28.407 (5.5989) kg/m². The majority of subjects were from Poland (377 (74.1%) subjects). A total of 397 (78.0%) subjects had a baseline body weight ≤100 kg and 112 (22.0%) subjects had baseline body weight >100 kg.

Table 22 Demographics Characteristics: 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%)
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%)

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

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

Source: Post-text Table 14.1.4.

Source: Table 11-3 in Clinical Study Report

Table 23 describes the baseline disease characteristics for the ITT Analysis Set. The baseline characteristics were similar between treatment groups in ITT. Overall, the mean PASI score was 21.2. One hundred and sixty-three (163) subjects (32.0%) had psoriasis arthritis (PsA), including 80 (31.3%) in the CT-P43 group and 83 (32.8%) in the EU-Stelara group. The mean of percent of body surface area affected was 25%. The median time since diagnosis of plaque-type psoriasis was comparable between

treatment groups (CT-P43: 17.81 years EU- Stelara: 15.56 years). Not many subjects (16.1%) had a history of prior biologic use approved for psoriasis treatment.

Table 23. Baseline Disease Characteristics in ITT Analysis Set

Characteristics	CT-P43 N=256	EU-Stelara N=253	Total N=509
Time since first diagnosis of plaque-type psoriasis (year)			
Mean $\pm$ SD	17.81 $\pm$ 12.14	15.56 $\pm$ 11.56	16.69 $\pm$ 11.90
Median	16.22	14.10	15.15
Min; Max	0.8; 59.2	0.4; 60.1	0.4; 60.1
Presence of Psoriasis Arthritis at Screening, n (%)			
Yes	80 (31.3)	83 (32.8)	163 (32.0)
No	176 (68.8)	170 (67.2)	346 (68.0)
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)
PASI score at Baseline			
Mean $\pm$ SD	21.51 $\pm$ 7.94	20.88 $\pm$ 8.00	21.19 $\pm$ 7.97
Median	19.7	18.8	19.2
Min; Max	12.0; 50.3	12.0; 56.7	12.0; 56.7
Percent of body surface area affected			
Mean $\pm$ SD	26.05 $\pm$ 14.15	24.25 $\pm$ 13.19	25.15 $\pm$ 13.70
Median	23.0	21.0	21.0
Min; Max	10.0; 90.0	10.0; 74.5	10.0; 90.0

Source: Table 14.1.8 in Clinical Study Report and Reviewer's Analysis

Analysis of Primary Clinical Endpoint(s)

Primary Analysis for the Primary Efficacy Endpoint

Table 24 shows the applicant's primary efficacy analysis results for the primary efficacy endpoint, the mean percent improvement from baseline in PASI score at Week 12. The primary efficacy analysis was conducted on the mITT Set using an ANCOVA model 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, coupled with MI with the MAR assumption for missing data handling. The point estimate (2.05) and 90% CI for the estimate of treatment difference ([-0.23, 4.32]) were entirely within the predefined similarity margin of -10% to 10%, which demonstrated no clinically significant difference between the CT-P43 and EU-Stelara groups in the primary endpoint for the mITT Set. A supportive analysis was conducted using the PPS and the

result is consistent with the primary efficacy analysis result (90% CI: [-0.29, 4.29] for the PPS). The reviewer replicated the applicant's analysis results.

Table 24. Primary and Supportive Efficacy Results for the Primary Efficacy Endpoint (ANCOVA) – Multiple Imputation on Modified ITT Set (Primary) and PP Set (Supportive)

	n	LS Mean (SE)	Estimate of Treatment Difference (%)	90% CI of Treatment Difference (%)
Modified ITT Set				
CT-P43	256	77.93 (1.771)	2.05	(-0.23, 4.32)
Stelara	253	75.89 (1.739)		
PPS				
CT-P43	252	78.06 (1.767)	2.00	(-0.29, 4.29)
Stelara	244	76.06 (1.735)		

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ITT, intent-to-treat; LS, least squares; MAR, missing at random; mITT, modified intent-to-treat; PASI, Psoriasis Area and Severity Index; PPS, per-protocol set; 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 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 was 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. Imputation with the MAR assumption was used for missing data imputation for the mITT Set only. Since there was no missing PASI total score in PPS, the analysis was conducted without imputation. Adjusted LS means and SE, estimate of treatment difference [CT-P43 – Stelara] and 90% CI were calculated from the ANCOVA model.

Source: Post-text Table 14.1.9.

Source: Table 11-7 in the Applicant's Clinical Study Report and reviewer's analysis

Potential Effects of Missing Data

Sensitivity Analysis for Primary Efficacy Endpoint

To assess the robustness of the primary efficacy analysis result based on MI with the MAR assumption for missing data handling, the applicant conducted a sensitivity analysis using tipping point analysis under MNAR scenario for the primary efficacy endpoint in the mITT Set. In the tipping point analysis, imputed values for missing data of 5 subjects in the EU-Stelara treatment group were shifted gradually from the imputed values by MI under MAR by treatment groups (CT- P43 vs. EU-Stelara) to make MNAR scenarios while there were no missing cases in the CT- P43 treatment group. The shift occurred within the range of percent improvement from baseline in PASI score at Week 12 (0 to 100) and all possible scenarios were entirely within the equivalence margin of -10% to 10% (Table 25).

Table 25. Sensitivity Analysis Result for Primary Efficacy Endpoint:

Tipping Point Analysis on mITT Set

Shift for CT-P43	Shift for EU-Stelara (%)										
	-100	-80	-60	-40	-20	0	20	40	60	80	100
N/A	3.64 (1.08, 6.19)	3.52 (1.00, 6.03)	3.21 (0.78, 5.64)	2.83 (0.48, 5.18)	2.44 (0.14, 4.74)	2.05 (-0.23, 4.32)	1.77 (-0.50, 4.05)	1.69 (-0.59, 3.97)	1.67 (-0.61, 3.96)	1.67 (-0.61, 3.96)	1.67 (-0.61, 3.96)

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 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. Imputed missing values were shifted from -100 to 100 by 20. When the imputed value is over 100 or under 0, it was replaced with 100 or 0 respectively. Final statistical inference based on Rubin's rule was displayed by combining the results from each set of imputed datasets. Estimate of treatment difference [CT-P43 – EU-Stelara] and 90% CI were calculated from the ANCOVA model.

Source: Section 5.3.5.3 Post-hoc Table 3.05 and reviewer's analysis

To further test the robustness of the primary analysis, the Applicant also conducted Best-Worst Case and Worst-Best Case sensitivity analyses (Table 26) - an ANCOVA analysis on the assumption that the missing values in CT-P43 are imputed with "100" percent and the ones in EU-Stelara are imputed with "0" percent (Best-Worst Case Scenario) and vice versa (Worst-Best Case Scenario). The 90% CI of the mean percent change from baseline in PASI at Week 12 between the two treatment groups all falls within the margin of $\pm 10\%$. Hence, all the sensitivity analysis results confirmed the result from the primary efficacy analysis.

Table 26. Sensitivity Analyses Results for Primary Efficacy Endpoint (ANCOVA):

Best-Worst and Worst-Best Case on Modified ITT Set

	n	LS Mean (SE)	Estimate of Treatment Difference (%)	90% CI of Treatment Difference (%)
Best-Worst Case Scenario				
CT-P43	256 (0)	78.00 (1.985)	3.64	(1.08, 6.19)
Stelara	253 (5)	74.37 (1.949)		
Worst-Best Case Scenario				
CT-P43	256 (0)	77.98 (1.773)	1.67	(-0.61, 3.96)
Stelara	253 (5)	76.31 (1.740)		

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; mITT, modified Intent-to-Treat; LS, least squares; PASI, Psoriasis Area and Severity Index; SE, standard error.

Source: Post-text Table 14.2.1.2a.

Source: Table 11-9 in the Applicant's Clinical Report and reviewer's analysis

Assay Sensitivity and Constancy

Efficacy data from Study CT-P43 3.1 were compared to the results from Stelara studies. These studies employed the same dosage regimen as that used in Study CT-P43 3.1 and the key eligibility criteria were similar to those of Study CT-P43 3.1. All the studies had key eligibility criteria: Plaque-type psoriasis diagnosed >6 months prior, and Plaque-type psoriasis covering at least 10% of total BSA. The Study CT-P43 3.1 had more restrictive criteria (PASI score of ≥ 12 , sPGA score of ≥ 3).

The efficacy results of the mean percent improvement from baseline in PASI score at Weeks 12 and 28, the timepoints where efficacy results of Stelara studies are publicly available, in Study CT-P43 3.1 are well aligned with results from Stelara studies (Table 27).

Table 27. Comparison of Efficacy between Study CT-P43 3.1 and Stelara Studies with Similar Design in Psoriasis Patients

Study	Regimen	Mean percent improvement from baseline in PASI score at Week 12; Mean $\pm$ SD		Mean percent improvement from baseline in PASI score at Week 28; Mean $\pm$ SD		Key eligibility criteria
		Ustekinumab 45 mg	Ustekinumab 90 mg	Ustekinumab 45 mg	Ustekinumab 90 mg	
CT-P43 3.1 Section 5.3.5.3 Post-hoc Table 3.01	• Ustekinumab SC of 45 or 90 mg at W0 and W4, then every 12 weeks	85.37 $\pm$ 15.494 (CT-P43) 84.32 $\pm$ 17.906 (EU-Stelara)	88.40 $\pm$ 12.142 (CT-P43) 82.80 $\pm$ 15.978 (EU-Stelara)	94.77 $\pm$ 8.865 (CT-P43) 93.20 $\pm$ 13.698 (EU-Stelara)	96.04 $\pm$ 6.089 (CT-P43) 90.20 $\pm$ 13.722 (EU-Stelara)	• Plaque-type psoriasis diagnosed >6 months prior • Plaque-type psoriasis covering at least 10% of total BSA • PASI score of ≥ 12 • sPGA score of ≥ 3
PHOENIX 1 Leonardi <i>et al.</i> , 2008	• Ustekinumab SC of 45 or 90 mg at W0 and W4, then every 12 weeks	75.6 $\pm$ 27.04	77.2 $\pm$ 23.67	80.3 $\pm$ 23.65	85.2 $\pm$ 19.40	• Plaque-type psoriasis diagnosed >6 months prior • Plaque-type psoriasis covering at least 10% of total BSA
PHOENIX 2 Papp <i>et al.</i> , 2008		77.0 $\pm$ 25.78	82.1 $\pm$ 22.57	79.8 $\pm$ 23.70	84.8 $\pm$ 20.46	
Igarashi <i>et al.</i> , 2012	• Placebo at W0, W4 then Ustekinumab SC (45 or 90 mg) at W12 and W16 and every 12 weeks	73.1 $\pm$ 29.6	75.0 $\pm$ 29.0	N/A	N/A	

Source: Table 2.7.3-21 Module 2, Section 2.7.3 Summary of Clinical Efficacy

Analysis of Secondary Clinical Endpoint(s)**The PASI scores at Weeks 0, 2, 4, 8, 12, 16, 28, 40, and 52**

The PASI scores during Treatment Period I were generally similar between the CT-P43 and EU-Stelara groups in the mITT Set (Table 28).

Table 28. The PASI Score: Modified ITT Set

Visit Statistic	CT-P43 (N=256)	Stelara (N=253)	Estimate of Treatment	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		
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; ITT, intent-to-treat; 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.

Source: Post-text Table 14.2.2.1.

Source: Table 11-10 in the applicant's Clinical Study Report

Table 29 presents the PASI scores for Treatment Period II. While the PASI score at Week 16 and EOS seemed to be 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 mITT – Treatment Period II Subset during Treatment Period II and up to EOS.

Table 29. The PASI Score: Modified ITT – 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; ITT, intent-to-treat; PASI, Psoriasis Area and Severity Index; SD, standard deviation.

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

Source: Table 11-11 in the Applicant's Clinical Study Report.

The mean percent improvement from baseline in PASI score at Weeks 2, 4, 8, 16, 28, 40, and 52

The mean percent improvement from baseline in PASI score was generally similar between the CT-P43 and EU-Stelara groups in the mITT Set and PPS during Treatment Period I (details in Table 30).

Table 30: Percent Improvement from Baseline in PASI Score: Modified ITT Set

Visit	CT-P43	Stelara	Estimate of Treatment Difference (%)	95% CI of Treatment Difference (%)
Statistic	(N=256)	(N=253)		
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; ITT, intent-to-treat; 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.

Source: Post-text Table 14.2.2.2.

Source: Table 11-12 in the Applicant's Clinical Study Report.

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 mITT – Treatment Period II Subset during Treatment Period II and up to EOS (Table 31).

Table 31. Percent Improvement from Baseline in PASI Score:

Modified ITT – 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; ITT, intent-to-treat; 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 subjects who completed or discontinued study drug. Source: Post-text Table 14.2.2.2.

Source: Table 11-13 in the Applicant's Clinical Study Report.

The proportion of PASI 50/75/90/100 at Weeks 2, 4, 8, 12, 16, 28, 40, and 52

Table 32 shows that the proportions of subjects achieving PASI 50, PASI 75, PASI 90, and PASI 100 responses during Treatment Period I were generally similar between the CT-P43 and EU-Stelara groups in the mITT Set. 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.

Statistical Reviewer's Comment:

For PASI75 at Week 12, CT-P43 seems to have a higher proportion of responders (82.8%) than EU-Stelara (73.9%). The reported 95% CI of the risk difference between CT-P43 and EU-Stelara was [1.78, 16.02] (Table 32). While the 95% CI was used by the applicant for exploratory purpose, considering that 90% CI is usually used for a biosimilar study, the reviewer calculated the 90% CI for the risk difference, which is [2.93, 14.87]. Additional analyses of the secondary endpoints in Table 32 are consistent with the primary endpoint and the results support a demonstration that there are no clinically meaningful differences between CT-P43 and U.S.-Stelara.

CDTL Comment: From a clinical perspective, no clinically meaningful differences have been demonstrated in terms of efficacy because the primary endpoint 90% CI was contained within the prespecified margins. The PASI 75 endpoint is supportive. It should be noted that continuous endpoints tend to be more powerful than binary endpoints for the same underlying scale, which can translate into seemingly larger estimated treatment effects that may be random, due to the studies being underpowered for the binary endpoint comparisons.

Additionally, the secondary endpoints do not appear to show a pattern suggestive of a meaningful difference in PASI response between the two study arms (Table 32). These descriptive secondary endpoints support a demonstration that there are no clinically meaningful differences between CT-P43 and US-Stelara.

Table 32. Proportion of PASI 50/75/90/100 Responders: Modified ITT Set

Parameter Visit	CT-P43 (N=256) n (%)	EU-Stelara (N=253) n (%)	Estimate of Treatment Difference (%)	95% CI of Treatment Difference (%)
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PASI 50

Biosimilar Multidisciplinary Evaluation and Review (BMER)

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; ITT, intent-to-treat; NC, not calculated; PASI, Psoriasis Area and Severity Index.

Note: Percentages were calculated by using the number of subjects 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.

Source: Post-text Table 14.2.2.3.

Source: Table 11-14 in the Applicant's Clinical Study Report.

Table 33 shows that the proportions of subjects achieving PASI 50, PASI 75, PASI 90, and PASI 100 responses during Treatment Period II were generally similar among the CT-P43 maintenance, EU-Stelara maintenance, and Switched to CT-P43 groups in the mITT – 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.

Table 33. Proportion of PASI 50/75/90/100 Responders

Modified ITT – Treatment Period II Subset			
Parameter	CT-P43 Maintenance (N=253)	Stelara Maintenance (N=125)	Switched to CT-P43 (N=124)

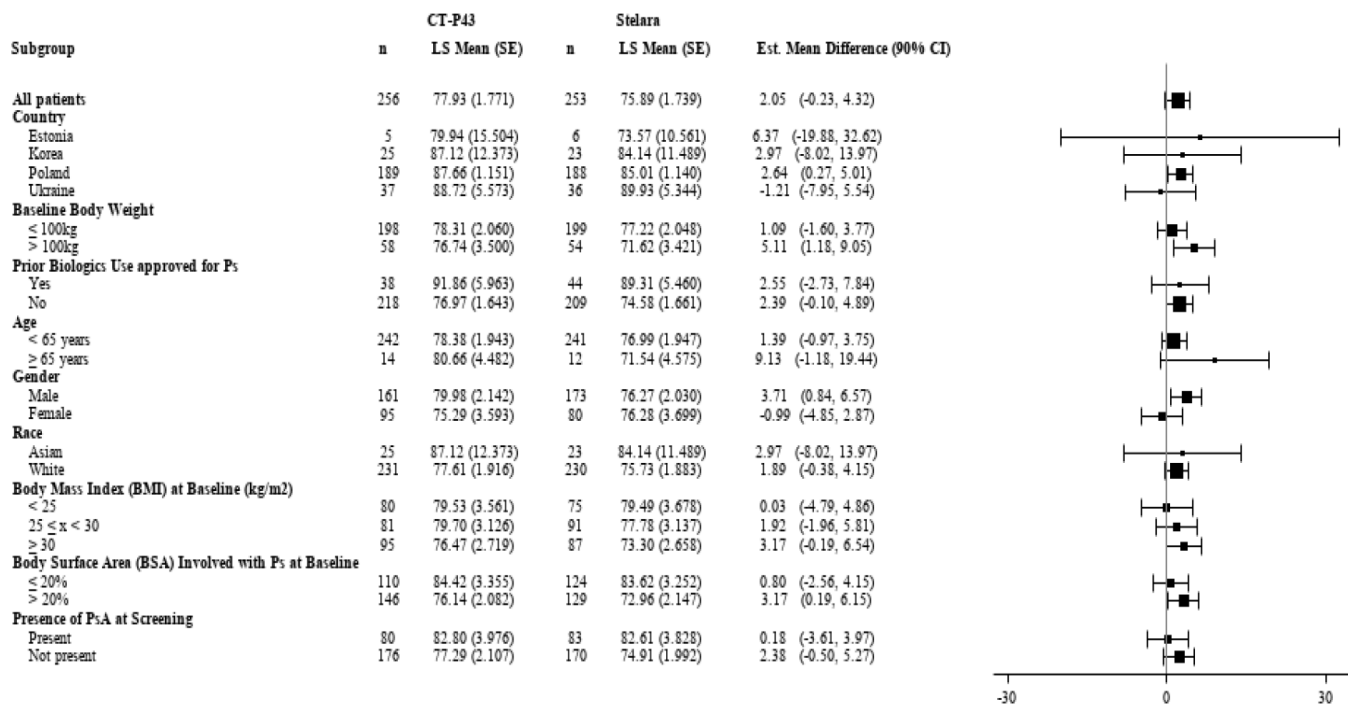
Number (%) of Patients			
PASI 50			
Week 16	250 (98.8%)	120 (96.0%)	120 (96.8%)
Week 28	250 (98.8%)	121 (96.8%)	123 (99.2%)
Week 40	246 (97.2%)	120 (96.0%)	123 (99.2%)
EOS	236 (93.3%)	118 (94.4%)	119 (96.0%)
PASI 75			
Week 16	225 (88.9%)	104 (83.2%)	105 (84.7%)
Week 28	244 (96.4%)	116 (92.8%)	116 (93.5%)
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; ITT, intent-to-treat; PASI, Psoriasis Area and Severity Index. Note: Percentages were calculated by using the number of subjects in the set as the denominator. Source: Post-text Table 14.2.2.3.

Source: Table 11-15 in the Applicant's Clinical Study Report.

Subgroup Analysis

Figure Subgroup Analysis for the Primary Efficacy Endpoint Percent Change from Baseline in PASI at Week 12, in mITT



Note: An ANCOVA was performed with treatment as the fixed effect and country, baseline body weight, prior biologic use approved for psoriasis treatment and baseline PASI score as covariates. Imputation with the MAR assumption was conducted for missing data. For the case that imputed value of percent improvement from baseline in PASI score at Week 12 is over 100, it was replaced with 100. If a covariate was used as subgroup, the variable was not used as covariates in ANCOVA model.

Abbreviations: LS, least squares; n, number of subjects received a study drug in each subgroup; NE, not estimable; Ps, psoriasis; SE, standard error.

Source: Section 5.3.5.3 Post-hoc Figure 3.03 in the Applicant's Clinical Study Report

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6.3. Review of Safety Data

6.3.1. Methods

To characterize safety, adverse events, laboratory examination, vital signs, hypersensitivity, and immunogenicity were reviewed. The primary study used to evaluate safety was the comparative clinical study CT-P43 3.1, as it provided controlled and blinded comparisons between EU-Stelara and CT-P43 in subjects with moderate to severe plaque psoriasis for up to 52 weeks. Safety data from the two pharmacokinetics (PK) similarity studies conducted in healthy volunteers, CT-P43 1.1 and CT-P43 1.2, were also briefly reviewed as supportive of the primary safety assessment.

Clinical Studies Used to Evaluate Safety

The Applicant submitted safety data from three clinical studies in support of the BLA, as listed in **Table 3** and summarized below. In all three clinical studies, subjects received 45 mg or 90 mg of either CT-P43, EU-Stelara, or US-Stelara. The primary safety data were derived through the conduct of Study CT-P43 3.1. The remaining two studies, CT-P43 1.1 and CT-P43 1.2, were single-dose PK similarity studies in healthy male volunteers. The former of the two studies was conducted in New Zealand, and the latter exclusively enrolled Japanese male volunteers. As such, limited safety data for the intended population can be obtained from these two studies.

- CT-P43 1.1 was a randomized, double-blind, 3-arm, parallel group, single dose study in healthy male volunteers to assess the PK similarity of a 45 mg subcutaneous dose of CT-P43, EU-Stelara, or US-Stelara. For Part 1, 30 subjects were randomized to receive CT-P43 (n=14) or EU-Stelara (n=16) and evaluated up to Day 29. For Part 2, 241 subjects were randomized to receive CT-P43 (n=80), EU-Stelara (n=82) or US-Stelara (n=79) and evaluated up to Day 127. CT-P43 1.1 was meant to serve as a bridging study; however, the study failed to establish the PK similarity, as the upper bounds of the 90% CIs for AUC_{0-inf} were over the 125% acceptance range between CT-P43 and US-Stelara or CT-P43 and EU-Stelara.
- The second PK similarity study, CT-P43 1.2, which met the criteria for establishing the PK similarity, was a randomized, double-blind, 3-arm, parallel group, single dose study to compare the PK and safety of three formulation of ustekinumab (CT-P43, EU-Stelara and US- Stelara) in healthy Japanese male volunteers. The study randomized 331 subjects to receive a single dose of 45 mg SC injection of CT-P43 (n=114), EU-Stelara (n=110) or US-Stelara(n=107) and evaluated the subjects up to Day 113. Safety data from these two PK studies are included for completeness.
- The primary safety data were derived through the conduct of the clinical study CT-P43 3.1, which was a randomized, double blind, active controlled, parallel group study designed to compare efficacy and safety of CT-P43 and EU-Stelara in adults with moderate to severe psoriasis. This study randomized 509 subjects to receive CT-P43 (n=256) or EU-Stelara (n=253). The subjects received an initial dose of study drug 45 or 90mg administered subcutaneously, followed by another dose 4 weeks later, and then every 12 weeks thereafter up to Week 40. The subjects who weighed ≤100kg received 45 mg (1 injection of 45mg/0.5ml) of study drug by SC injection via PFS, and those who weigh >100kg received 90 mg (2 injections of 45 mg/0.5 ml) of study drug by SC injection via PFS.

The study had two treatment periods:

- Treatment Period I (TP1) (16 weeks, Week 0 - Week 15)
- Treatment Period II (TP2) (24 weeks, Week 16 – Week 52)

The subjects that achieved at least PASI 50 at Week 12 entered TP2 in all groups. Prior to dosing at Week 16, all subjects underwent the second randomization process. The subjects who were initially randomized to EU-Stelara for TP1 were randomized again in a ratio of 1:1 for TP2 to either continue EU-Stelara or switch to CT-P43. All subjects who

were initially randomized to the CT-P43 group for TP1 continued their treatment for TP2 with CT-P43. At Week 28, the subjects who achieved at least PASI 75 continued further study drug administration in all groups.

Extent of Exposure

The safety database includes a total of 588 participants who received at least one dose of CT-P43 (208 healthy individuals and 380 subjects with PsO).

- Healthy subjects: 602 participants received a single dose of 45 mg/0.5mL product subcutaneously.
 - o CT-P43, n=208 (n=14, evaluated up to Day 29; n=80, evaluated up to Day 127; n=114, evaluated up to Day 113)
 - o EU-Stelara, n=208 (n=116, evaluated up to Day 29; n=80, evaluated up to Day 127; n=110, evaluated up to Day 113)
 - o US-Stelara n=186 (n=79, evaluated up to Day 127; n=107, evaluated up to Day 113)
- Subjects with psoriasis: 509 subjects received at least one dose of 45mg/0.5mL product subcutaneously followed by another dose 4 weeks later, and then every 12 weeks thereafter up to Week 40. Those receiving EU-Stelara were re-randomized 1:1 to receive either CT-P43 or EU-Stelara at Week 16.
 - o CT-P43, n=256 (during Treatment Period 1); n=377 (during Treatment Period 2)
 - o EU-Stelara, n=253 (during Treatment Period 1); n= 125 (during Treatment Period 2)

Median treatment durations were comparable across the treatment groups in Study CT-P43 3.1 (Table 18). A similar proportion of subjects in the CT-P43 treatment group received all 5 doses of the study medication (95.3%), compared to the EU-Stelara (96.8%) group. The mean number of doses received was 5.0 for the EU-Stelara (TP1) - EU-Stelara (TP2) and EU-Stelara (TP1) - CT-P43 (TP2) treatment groups and 4.9 for the CT-P43 (TP1) – CT-P43 (TP2) groups.

Table 34: Exposure to Study Medications, CT-P43 3.1 (Safety Analysis Set)

		Stelara (TP1) - Stelara (TP2)	Stelara (TP1) -CT-P43 (TP2)	CT-P43 (TP1) -CT-P43 (TP2)	Stelara (TP1)	CT-P43 (TP1)
Number of subjects		125	124	253	4	3
Number of Injections (Duration of Exposure in Weeks)	Mean	5 (52)	5 (52)	4.9 (51)	1.5 (10)	1.7 (12)
	Std Dev	0.3 (3)	0.2 (2)	0.3 (3)	0.6 (6)	0.6 (6)
	Min	3 (28)	4 (40)	3 (28)	1 (4)	1 (4)
	Quantiles 25	5 (52)	5 (52)	5 (52)	1 (4)	1 (4)
	Median	5 (52)	5 (52)	5 (52)	1.5 (10)	2 (16)
	Quantiles 75	5 (52)	5 (52)	5 (52)	2 (16)	2 (16)
	Max	5 (52)	5 (52)	5 (52)	2 (16)	2 (16)

	N Missing	0	0	0	0	0
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Source: Clinical Reviewer

Clinical Reviewer's Comment: The extent of exposure to the study drug is comparable across the treatment groups throughout the study period and is adequate to support a comparative safety assessment.

Categorization of Adverse Events

For the CT-P43 1.1, CT P-43 1.2, and CT-P43 3.1 studies, at every study visit the subjects were asked a “standard question to elicit any medically related changes in their well-being.” They were also asked if they had been “hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).”

The Applicant reported that the Investigators’ verbatim terms were converted to preferred terms (PTs), according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, and the Medical Dictionary for Regulatory Activities (MedDRA). The Applicant defined treatment-emergent AE (TEAE) as any untoward medical occurrence in a subject after administration of a drug, whether or not it was considered drug-related. The Applicant also defined any occurrence that was new in onset or aggravated in intensity or frequency from the baseline condition and abnormal results of diagnostic procedures including laboratory test abnormalities as AEs, if they resulted in discontinuation from the study, required therapeutic intervention or diagnostic evaluation, or were associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact. Disease progression of psoriasis and PsA was not recorded as an AE or SAE. The final monitoring for adverse event was conducted at the EOS visit, which was 12 weeks after the last administration of the study drug.

The Applicant reported that the AEs were monitored from the date the subject signed the Informed Consent Form (ICF) until the end-of-study (EOS) visit. All the AEs were reportedly followed until resolution or improvement to baseline, death, confirmed by the investigator that no further improvement could be expected, no more collection of clinical or safety data, or final database closure.

The intensity of an AE referred to the extent to which an AE affected the subject’s daily activities. The intensity of the AE was graded based on the CTCAE v5.0, based on the following general:

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

Grade 2: Moderate: minimal, local, or non-invasive intervention indicated or limiting age-appropriate instrumental activities of daily living

Grade 3: Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated or disabling or limiting self-care activities of daily living

Grade 4: Life-threatening consequences: urgent intervention indicated

Grade 5: Death related to AE

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

- Resulted in death
- Was immediately life-threatening
- Required in subject hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Was a congenital anomaly/birth defect
- Important medical events that could have required medical or surgical intervention to prevent one of the outcomes listed in this definition.

Adverse events of special interest including opportunistic infections and immune-based adverse effects were summarized using grouped MedDRA codes, in addition to presentation of individual adverse event preferred terms. Immune-based adverse effects included injection-site reactions (ISRs), adverse events that fulfill Sampson Criteria, and adverse events identified as potential hypersensitivity/anaphylactic reactions using a system MedDRA standardized MedDRA query (SMQ) that occur in relation to administration of the study drug.

Clinical Reviewer's Comment: The Applicant's definition of TEAEs and categorization of AEs is acceptable.

Safety Analyses

Safety assessments were also performed based on immunogenicity, hypersensitivity monitoring, body weight, vital sign measurements (including blood pressure, pulse and respiratory rates, and body temperature), interferon-gamma release assay (IGRA), chest X-ray, hepatitis B and C, physical examination findings, clinical laboratory analyses, ECGs, AEs (including serious adverse events [SAEs]), adverse events of special interest (AESIs: infections or serious infections, injection site reactions, hypersensitivity reactions, and malignancies), pregnancy tests, prior and concomitant medications, local site pain using 100 mm VAS, and signs and symptoms of tuberculosis. Human immunodeficiency virus status was tested to determine subject's eligibility.

Quality and Integrity of Safety Data

Clinical Reviewer's Introductory Comment on Data Quality: Based on the ADAE.xpt file, the adverse events (AEs) and serious adverse events (SAEs) initially appeared to have been appropriately defined, coded, and categorized by the Applicant during the CT-P43 development program. However, review of select adverse event narratives, case report forms (CRFs), and subject updates received from the Applicant after Information Request revealed several instances, where AEs were inappropriately defined or coded or where AEs were omitted. There were instances, where the subjects received treatment-emergent medications without noting concomitant adverse events that led to such medications or where subject narratives noted no therapeutic measures for the AEs, when it is noted elsewhere that specific medications for the AEs had been administered. Below some of the examples are discussed:

- Subject (b) (6) was a 43 year-old female in the CT-P43 maintenance group. She had a medical history of caesarian section, hypertension, psoriasis, and psoriatic arthritis. Her previous use of systemic medications included isotretinoin

(unknown duration), 2 months of acitretin (discontinued 2 years prior to starting the study), 2 weeks of cefuroxime (discontinued more than 2 years prior to starting the study), and 16 months of cyclosporine (discontinued 9 months prior to starting the study). Her concomitant systemic medications included levenorgestrel and ramipril.

On Day 208, she was noted by the Applicant to have a Grade 3 TEAE of “hypersensitivity” PT (“Reported Term for the Adverse Event”). However, the Applicant stated in a more detailed narrative in response to an IR that headache was the “only reported sign or symptom of the hypersensitivity” reaction noted by the Investigator. The Investigator noted the intensity of the headache to be severe, and the subject took ketoprofen for 40 days for the TEAE. The event of “hypersensitivity” was considered by the Investigator to be related to the study drug. The subject received her last dose of CT-P43 at her Week 28 Visit on Day 196. The headache persisted until Day 249.

The Applicant reported in the AE narrative that the subject discontinued the study drug before her Week 40 dose due to the reason of “withdrawal by patient.” The Appendix Table 2.7.4-22 (Figure 9) lists the following as “Reason in detail” for “Reason for study drug discontinuation”: “The patient informed the physician about study drug discontinuation due to AE (chronic headache).” The subject’s narrative was not included in “Narratives for Deaths and Serious and Certain Other Significant Adverse Events” (Figure 10), and the subject’s case report form (CRF) was not submitted along with other CRFs for subjects with discontinuations or withdrawals, due to AEs.

Figure 9: Excerpt from the Applicant's Table for Reason for Study Discontinuation

7 Appendix

Table 2.7.4-22: Summary of Primary Reason for Study Drug Discontinuation in Study CT-P43 3.1 Treatment Period II (Safety Population – Treatment Period II Subset)

Patient	Age/Sex/ Race	Treatment group	Reason for study drug discontinuation	Reason in detail
(b) (6)	43/F/W	CT-P43 Maintenance	Withdrawal by patient	The patient informed the physician about study drug discontinuation due to AE (chronic headache).
	62/F/W		Withdrawal by patient	The detailed reason is unable to be confirmed.
	24/M/W		Withdrawal by patient	The patient contacted the site on (b) (6) and withdrew their consent to participate in the study due to permanent relocation.
	38/F/W		Withdrawal by patient	The detailed reason is unable to be confirmed.
	36/M/AS		Withdrawal by patient	The patient refused to procedures/observations and withdrew the consent.
	42/F/W		Lost to follow-up	The site tried to contact the patient when the patient did not visit the site at Week 40 but the patient did not answer the phone.
	72/M/W		Adverse event	The patient experienced a Grade 2 non-serious TEAE of prostatic mass. The event was considered by the investigator to be unrelated to the study drug.
	34/M/W		Adverse event	The patient experienced a Grade 2 non-serious TEAE of hepatitis B surface antigen positive. The event was considered by the investigator to be unrelated to the study drug.
	55/M/W		Adverse event	The patient experienced a Grade 2 non-serious TEAE of hepatitis B. The event was considered by the investigator to be unrelated to the study drug.
	37/M/W		Death	The patient experienced a Grade 5 myocardial infarction and fell on the street on (b) (6). The event was considered by the investigator to be unrelated to the study drug.

Source: CTD Module 2, Section 2.7.4, Summary of Clinical Safety

Figure 10: Applicant's Table from 5.3.5.1, Study CT-P43 3.1 Final Clinical Study Report

14.3.3 Narratives of Deaths and Other Serious and Certain Other Significant Adverse Events			
One patient died during the study. A total of 18 TESAEs were reported in 17 patients, and 7 patients discontinued from the study due to a TEAE during the study. Narratives for these patients are in Appendix 16.2.7.1 .			
Patient Number	Death	TESAE	TEAE Leading to Study Drug Discontinuation
(b) (6)	No	Yes	Yes
	No	No	Yes
	No	Yes	No
	No	Yes	No
	No	Yes	No
	No	Yes	No
	No	No	Yes
	No	Yes	No
	No	Yes	No
	No	No	Yes
	No	Yes	No
	No	Yes	No
	Yes	Yes	Yes
	No	Yes	No
	No	Yes	No
	No	Yes	No
	No	No	Yes
	No	No	Yes
	No	Yes	No
	No	Yes	No
	No	Yes	No

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

Source: 14.3.3 of CTD Module 5.3.5.1, Study CT-P43 3.1 Final Clinical Study report

Clinical Reviewer's Comment: Given that the headache was the "only reported sign or symptom," this Grade 3 TEAE should have been noted as headache PT, not hypersensitivity PT. Since the Investigator believed the Grade 3 TEAE to be related to the study drug and coded it as "hypersensitivity," it is likely that the subject discontinued due to the AE. Table 2.7.4-22 confirms that the headache was the patient's reason for the study drug discontinuation. The Applicant did not submit the patient's CRF, which is required by 21 CFR 314.50(f).

- Subject (b) (6) was a 62-year-old white female in the CT-P43 maintenance group. Her medical history included hypertension, hyperthyroidism, myocardial infarction, percutaneous coronary intervention, cholelithiasis, hypercholesterolaemia, obesity, osteoarthritis, plaque psoriasis, psoriatic arthritis, asthma, latent tuberculosis, and psoriatic arthropathy. She experienced during TP1 a Grade 2 TEAE of chest pain PT (pain in the precordial area), for which she received treatment-emergent medications in the form of clopidogrel bisulfate and intravenous administration of paracetamol. Per the AE narrative provided by the Applicant, "(i)t is not known from the case report form if therapeutic measures were administered to treat the event," even though the subject's CRF (page 3010, CTD 5.3.5.1, Section 16.3.1) notes that the subject received medication for this AE.

Throughout the study, the subject also had 3 episodes of Grade 3 TEAEs of headache PT (headache syndrome). The investigator deemed the TEAEs to be related to the study drug, and 2 of the 3 episodes resolved after intramuscular metamizole. The study drug was withdrawn after the 3rd episode, but the subject was followed until the end of the study (EOS) visit. However, the Appendix Table 2.7.4-22 (Figure 9) lists “withdrawal by patient” as the “(r)reason for study drug discontinuation” and the following for the “(r)reason in detail”: “The detailed reason is unable to be confirmed.”

In the AE narrative, the Applicant reported that the headaches had resolved. In the subject update provided by the Applicant after an Information Request, it was reported that the subject continued to experience severe headaches, which are still ongoing. There are times when the number of episodes can be as high as 5 per week. These episodes are unpredictable and tend to coincide with sudden increases in systolic blood pressure, requiring ad hoc use of sublingual captopril.

Clinical Reviewer’s Comment: The subject received two medications during the TEAE of precordial chest pain, and the AE narrative stated that it was “not known” if therapeutic measures were administered. The Applicant’s Summary of Clinical Safety reported that the subject’s reason for study drug discontinuation was “withdrawal by patient,” rather than the recurrent episodes of Grade 3 headache, and that the detailed reason “could not be confirmed,” even though the reason was specified at the time of the study drug discontinuation. The AE narrative also stated that the headaches were resolved, even though the subject was followed up to 92 days after the study drug discontinuation (until EOS) and the update stated that these episodes had not resolved and had been frequently recurring.

In Section 1.2.1.1 of CTD Module 2, Section 2.7.4, Summary of Clinical Safety, the Applicant stated that during TP2 the number of subjects discontinued the study drug due to AEs is 5: “(3 [1.2%], 1 [0.8%] and 1 [0.8%] patients, respectively)” in the CT-P43 maintenance, EU-Stelara maintenance, and Switched to CTP43 groups. In the Appendix Table 2.7.4-22 (Figure 9), the Applicant lists the following 3 subjects in the CT-P43 maintenance group for study drug discontinuation due to AEs: (b) (6) for prostatic mass; (b) (6) for hepatitis B surface antigen positivity; and (b) (6) for hepatitis B. The two subjects (b) (6) who discontinued due to Grade 3 headache and Grade 3 “hypersensitivity” headache are not included and said to have discontinued due to “withdrawal by subject” (Figure 9).

In Section 14.3.3 of CTD Module 5.3.5.1, Study CT-P43 3.1 Final Clinical Study report (Figure 10), the Applicant reported that the number of subjects who discontinued the study drug due to AEs is 7 (5 subjects from the CT-P43 maintenance group; 1 from the EU-Stelara maintenance group; and 1 from EU-Stelara – CT-P43 switching group). Among the 5 subjects in the CT-P43 maintenance group, (b) (6) with Grade 3 headache and (b) (6) with fatal myocardial infarction are included, in addition to the 3 subjects mentioned above. The subject (b) (6) with the “hypersensitivity” headache is not included in this total number for either Figure 9 or Figure 10.

Clinical Reviewer’s Comment: There is discrepancy in the total numbers and reasons for study drug discontinuation presented in the narratives and tables provided by the Applicant throughout the Application.

- Subject (b) (6) was a 41-year-old Asian male in the CT-P43 maintenance group. His medical history included plaque psoriasis. His prior medication included one-day use of topical tacrolimus monohydrate, which he discontinued 46 days prior to starting CT-P43. The subject experienced during TP1 a Grade 2 TEAE of dyspepsia and a Grade 1 TEAE of “myalgia (abdomen)” on the same day. He was given FESTAL (cellulase ap 3; pancreatin; simeticone; ursodeoxycholic acid) as treatment. During TP2, he had as SAE of colon adenoma, for which endoscopy was performed to remove colon tubular adenoma during a 2-day hospitalization. He also had a Grade 1 TEAE of acute hepatitis, not otherwise specified, for which he received GODEX (adenine hydrochloride; bifendate; carnitine orotate; cyanocobalamin; liver extract; pyridoxine hydrochloride; riboflavin).

*Clinical Reviewer’s Comment: Given that this subject experienced dyspepsia and was treated with FESTAL including ursodeoxycholic acid, commonly used to help digestion, especially of fatty meals, the abdominal pain experienced on the same day should not have been coded as “myalgia” PT (of abdomen). Of note, the combination product the subject received during TP2 for acute hepatitis is commonly used for treatment of fatty liver disease, liver cirrhosis, drug-induced liver injury, and viral hepatitis. The review of his CRF, concomitant medications, and AE narratives suggests that this subject had TEAEs of dyspepsia, abdominal pain, and acute hepatitis that was unlikely from a viral origin. This subject’s SAE of colon adenoma is further discussed in **Serious Adverse Events**.*

- Subject (b) (6) was a 42 year-old female in the CT-P43 maintenance group with a past medical history of plaque psoriasis and psoriatic arthritis. Her prior use of systemic medications documented was for psoriasis and included 2 months of methotrexate (discontinued 11 years prior to starting the study), 10 days of clemastine fumarate (antihistamine discontinued 9 years prior to starting the study), and 17 months of bimekizumab (discontinued 12 months prior to starting the study). During TP1 she received betahistine hydrochloride for dizziness and mebeverine for irritable bowel syndrome, neither of which was listed as TEAEs; no TEAEs were reported for this patient. The Applicant included that the subject had “dizziness-undiagnosed” and “irritable bowel syndrome- not diagnosed” in the patient’s “Reported Term for the Medical History” file (admh.xpt). There was no documentation of treatment medications for these conditions prior to starting the study.

*Clinical Reviewer’s Comment: There was omission of the TEAEs of “dizziness” and “irritable bowel syndrome” for this subject. Listing of these “undiagnosed” conditions in the subject’s medical history was likely done after the TEAEs occurred. Regardless, any worsening or flare of even preexisting conditions should have been documented as TEAEs. See **Categorization of Adverse Events**.*

- Subject (b) (6) was a 40-year-old white female in the CT-P43 maintenance group, and her medical history included acne, proteinuria, plaque psoriasis, blood iron decreased, central obesity, hypercholesterolaemia, optic atrophy, and tachyarrhythmia. Her prior systemic medication use included a 21-day use of cyclosporine (stopped 105 days prior to the study), 241-day use of ferrous sulfate (6

days prior to the study), and 55-day use of EDP 1815 (stopped 127 days prior to the study), and she was not on any systemic medications at the beginning of the study. On Day 27, she started atorvastatin for hypercholesterolemia, as well as metformin for a TEAE of insulin resistance. The subject had hypercholesterolemia at Baseline, which was stable throughout the study, but had notable increases in serum triglyceride levels from her Baseline (1.82mmol/L at Screening and 2.11mmol/L on Day 1 to as high as 4.31mmol/L on Day 113) that were not documented as a TEAE. She was also started on two treatment-emergent medications, betaxolol hydrochloride (Days 189-199) and verapamil (Day 200-ongoing), for tachycardia. Tachycardia was listed as having started in 2017 and ended before starting the study. It was not noted that the subject had been previously medicated for tachycardia. These treatment-emergent episodes of tachycardia were not documented as TEAEs.

Clinical Reviewer's Comment: There was omission of these TEAEs of hypertriglyceridemia and tachycardia for this subject. A new adverse event of hypertriglyceridemia and worsening or flare of the previously existing tachycardia should have been documented as TEAEs.

- Subject (b) (6) was a 44-year-old white male in the Switched to CT-P43 group (discussed in detail under Serious Adverse Events). On Day 249 on CT-P43 treatment he experienced a Grade 3 SAE of respiratory failure. Per SUSPECT ADVERSE REACTION REPORT submitted by Applicant for the respiratory failure, "the action taken with the study drug was drug withdrawn." However, in the Appendix Table 2.7.4-22 (Figure 11), the Applicant lists that the TEAE of subarachnoid hemorrhage on EU-Stelara during TP1 as the reason for his study drug discontinuation.

Figure 11 Reason for Study Drug Discontinuation for (b) (6)

Patient	Age/Sex/Race	Treatment group	Reason for study drug discontinuation	Reason in detail
(b) (6)	48/M/W	Switched to CT-P43	Withdrawal by patient	The site contacted the patient on (b) (6) but the patient could not provide an exact date when he will be able to come to site due to personal reason. The site tried to contact him afterwards of no avail.
	44/M/W		Adverse event	The patient experienced a Grade 3 serious TEAE of subarachnoid haemorrhage. The event was resolved and considered by the investigator to be unrelated to the study drug.

Sources: Final CSR CT-P43 3.1 Post-text Table 14.1.1, Listings 16.2.1.1, 16.2.2.3, 16.2.7.1, 16.2.7.2, 16.2.7.3a and 16.2.7.4.

Abbreviations: AE, adverse event; AS, Asian; F, female; M, male; TEAE, treatment-emergent adverse event.

Clinical Reviewer's Comment: Here, again discrepancy is noted in the reported reason for the subject's discontinuation of the study drug in the various sources of data provided by the Applicant.

The Applicant reported that the AEs were monitored from the date the subject signed the Informed Consent Form (ICF) until the end-of-study (EOS) visit. All the AEs were reportedly followed until resolution or improvement to baseline, death, confirmed by the investigator that no further improvement could be expected, no more collection of clinical or safety data, or final database closure.

Clinical Reviewer's Comment: Information Request revealed several instances, where subjects had undefined neoplasms as TEAEs and no further clinical updates were available as to determine whether these neoplasms were given further work-up or histopathological diagnoses. Subject (b) (6) had a TEAE of prostatic mass PT; Subject (b) (6)

(b) (6) had a TEAE of breast mass PT; and Subject (b) (6) had a TEAE of cervical dysplasia PT with LEEP excision. There are no definitive updates provided by the Applicant on the nature of these neoplasms. These subjects are discussed in more detail in the section Adverse Events of Special Interest under Malignancies.

Clinical Reviewer's Conclusion on the Quality and Integrity of the Safety Data: There are multiple instances of omission, inappropriate coding, and insufficient follow-up of TEAEs, as noted above. Also, description of the nature, status, or outcome of the TEAEs varied depending on the source of data provided by the Applicant. There may be more cases not captured by this review. Thus, the safety analyses shown here may not provide a reliable depiction of safety risks associated with CT-P43. Exhaustible examination of narratives, figures, and tables to cross-reference to determine consistency and validity for each data point for all TEAEs is not practicable. Therefore, lack of integrity in the study data compromises the assessment of clinical comparability on safety risk.

6.3.2. Major Safety Results

Relevant Characteristics of the Population Evaluated for Safety

Study CT-P43 1.1 enrolled healthy male volunteers in New Zealand, and Study CT-P43 1.2 enrolled healthy male volunteers in Japan. The demographics are presented in Table 41 and Table 42, respectively. The participants in Study CT-P43 1.1 were on average 29 years old and mostly White (71%). The participants in the Study CT-P43 1.2 were on average 35 years old and were all Asian (100%).

Clinical Reviewer's Comment: The demographic characteristics were similar across the treatment arms in both single-dose PK studies.

Study CT-P43 3.1 enrolled adults with moderate-to-severe psoriasis, and the subject demographics are presented in Table 19. The participants were mostly male (66%) and White (91%), with an average age of 42 years and average baseline weight of 86 kg. Ninety-one per cent of the participants were from Europe, with the remainder coming from South Korea. Baseline psoriasis characteristics assessed in terms of Baseline PASI are presented in Table 35. Baseline Disease Characteristics in ITT Analysis Set.

Table 35 Demographics for CT-P43 3.1 Study

Demographic Characteristics	TP1		TP2	
	EU-Stelara (n=253)	CT-P43 (n=256)	EU-Stelara (n=125)	CT-P43 (n=377)
Age				
0 <= Age <= 39	107 (42.3%)	106 (41.4%)	52 (41.6%)	157 (41.6%)
39 < Age <= 64	134 (53.0%)	136 (53.1%)	65 (52.0%)	203 (53.8%)
Age > 64	12 (4.7%)	14 (5.5%)	8 (6.4%)	17 (4.5%)

Demographic Characteristics	TP1		TP2	
	EU-Stelara (n=253)	CT-P43 (n=256)	EU-Stelara (n=125)	CT-P43 (n=377)
Mean	42.18	42.55	42.99	42.13
Standard Deviation	19	19	20	19
Sex				
F	80 (31.6%)	95 (37.1%)	39 (31.2%)	133 (35.3%)
M	173 (68.4%)	161 (62.9%)	86 (68.8%)	244 (64.7%)
Baseline Body Weight (kg)				
Mean	86	85	86	85
Standard Deviation	1.2	1.2	1.7	1.0
Race				
Asian	23 (9.1%)	25 (9.8%)	10 (8.0%)	34 (9.0%)
White	230 (90.9%)	231 (90.2%)	115 (92.0%)	343 (91.0%)
Ethnicity				
Hispanic or Latino	1 (0.4%)	1 (0.4%)	1 (0.8%)	1 (0.3%)
Not Hispanic or Latino	252 (99.6%)	255 (99.6%)	124 (99.2%)	376 (99.7%)
Country				
Poland	188 (74.3%)	189 (73.8%)	91 (72.8%)	283 (75.1%)
Ukraine	36 (14.2%)	37 (14.5%)	21 (16.8%)	52 (13.8%)
Korea, South	23 (9.1%)	25 (9.8%)	10 (8.0%)	34 (9.0%)
Estonia	6 (2.4%)	5 (2.0%)	3 (2.4%)	8 (2.1%)

Source: Clinical Reviewer

Clinical Reviewer's Comment: The demographic and disease characteristics, in terms of age, sex, race, ethnicity, and mean baseline body weight, were similar across the two treatment arms, EU-Stelara and CT-P43, for Treatment Period I (TP1) and for Treatment Period II (TP2).

Overall AE profile

The phase 3 clinical study, Study CT-P43 3.1, provides the main comparative data for the safety review. During TP1, the overall rate of TEAEs was higher for the CT-P43 treatment group (37.1% - 155 events in 95 subjects), compared to the EU-Stelara treatment group (29.6% - 108 events in 75 subjects) (Table 20). The overall rates of SAEs were similar 1.6% (4 subjects) for the CT-P43 treatment and 1.6% (4 subjects) for the EU-Stelara treatment groups. No subjects discontinued treatment due to an AE during TP1.

During TP2, TEAEs were reported in 34.0% (144 events in 86 subjects) for the CT-P43 maintenance, in 40.8% (78 events in 51 subjects) for the EU-Stelara maintenance and in 41.9% (95 events in 52 subjects) for the Switched to CT-P43 treatment groups. The overall rates of SAEs were similar in the CT-P43 maintenance, EU-Stelara maintenance (2.4%), and Switched to CT-P43 (1.6%) groups. However, slightly more subjects discontinued due to an AE in the CT-P43 maintenance group (2.0%) compared to the EU-Stelara maintenance (0.8%) and Switched to CT-P43 (TP2) (0.8%) groups (Table 36). The details for the discontinuations are discussed further in the section **Dropouts and Discontinuations** below.

Clinical Reviewer's Introductory Comments on Safety Analysis: In the safety analyses of the TEAEs for the main clinical comparability study, there were imbalances in hypertriglyceridemia, headaches/migraine, hypertension, Hepatobiliary SOC Disorders, Gastrointestinal SOC Disorders, and Neoplasm SOC Disorders with more cases reported in the CT-P43 treatment group, compared to the EU-Stelara treatment group. These TEAE imbalances were noted, despite similar Baseline characteristics, such as weight, BMI, age, sex, ethnicity (Table and Table), and prior use of immunosuppressants (Table). The subjects' medical history, in terms of cardiovascular disorders, hypertension, hepatobiliary disorders including steatohepatosis or steatohepatitis, hypertriglyceridemia, lipid disorders, and gastrointestinal disorders, and diabetes mellitus also showed similar rates of Baseline prevalence between CT-P43 and EU-Stelara treatment groups during TP1 and between CT-P43 maintenance and EU-Stelara maintenance treatment groups during TP2. (CT-P43 Post-hoc analysis - Study 3.1, Tables 1.12, 1.13, and 1.14, provided on March 14, 2024 by Celltrion, Inc.). The TEAE imbalances are discussed in more detail in the following sections: **Serious Adverse Events, Treatment Emergent Adverse Events, and Adverse Events of Special Interest under Malignancies.**

Table 36 Safety Summary for Study CT-P43 3.1 (Safety Analysis Set)

Treatment Emergent Adverse Events Description	Period 1		Period 2		
	Stelara (n=253)	CT-P43 (n=256)	Stelara (TP1)- Stelara (TP2) (N = 125)	Stelara (TP1) CT-P43 (TP2) (N = 124)	CT-P43 (TP1)- CT-P43 (TP2) (N = 253)
	n (%)	n (%)	n (%)	n (%)	n (%)
Any TEAE	75 (30%)	95 (37%)	51 (41%)	52 (42%)	86 (34%)
Severe TEAE (Grades 3, 4, 5)	11 (4.3%)	14 (5.5%)	7 (5.6%)	9 (7.3%)	9 (3.6%)
Treatment emergent SAE	4 (1.6%)	4 (1.6%)	3 (2.4%)	2 (1.6%)	5 (2.0%)
TEAEs leading to death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
TEAEs leading to treatment discontinuation	0 (0%)	0 (0%)	1 (0.8%)	1 (0.8%)	5 (2.0%)

Source: Clinical Reviewer

Deaths

Healthy Volunteers (Studies CT-P43 1.1 and CT-P43 1.2): There were no deaths reported in the two single-dose PK studies in healthy male volunteers.

Subjects with PsO (Study CT-P43 3.1): No subjects died during TP1. During TP2, one (0.4%) subject in the CT-P43 maintenance group died, due to a TEAE of myocardial infarction.

The deceased subject (b) (6) a 37-year-old White male in the CT-P43 maintenance group, experienced Grade 5 myocardial infarction and fell on the street on (b) (6) (69 days after the Week 28 dose). The subject had ongoing medical conditions of tobacco smoking and obesity and no other past medical history. He was not receiving any concomitant medications during the study but received Covid-10 Comirnaty vaccine doses (the first dose on

(b) (6) and second dose on (b) (6). His past treatment for psoriasis included phototherapy, acitretin, and various topical medications, including corticosteroids and tacrolimus 0.1%. The Applicant reported there was no other available information related to the cause of death. The event of myocardial infarction was considered by the Investigator to be unrelated to the study drug.

*Clinical Reviewer's Comment: Although the subject had risk factors for myocardial infarction, such as obesity and smoking, this reviewer's determination on causality of death is that it's possibly related to the study drug. This is based on the overall safety data imbalance with disproportionate worsening of cardiovascular risk factors, such as hypertension, hypertriglyceridemia, and hyperglycemia, observed in the CT-P43 treatment group. This imbalance in the safety data is further discussed in the sections: **Treatment Emergent Adverse Events and Serious Adverse Events**.*

Serious Adverse Events (SAEs)

Healthy Volunteers (Studies CT-P43 1.1 and CT-P43 1.2): Four SAEs occurred during the single-dose PK studies in healthy volunteers, and all the cases occurred in Study CT-P43 1.1. In the US-Stelara treatment group, 1 participant experienced clavicle fracture from a fall 36 days after the dosing, and 1 participant experienced neck injury from mountain biking 55 days after the dosing. In the CT-P43 treatment group, 1 participant experienced right thumb laceration after a "circular saw accident" 99 days after the dosing, and 1 participant experienced lower abdominal pain 6 days after the dosing. The participant with the abdominal pain, a 19 year-old White male, also had nausea and vomiting. After having an unremarkable abdominal CT scan, he was given an oral antibiotic, and the SAE was eventually reported as resolved.

The three SAEs involving clavicle fracture, neck injury, and right thumb laceration were deemed unrelated. Of note, the lower abdominal pain was deemed by the Investigator as possibly related to the drug.

Clinical Reviewer's Comment: The Applicant's determination of causality for these SAEs is reasonable.

Subjects with PsO (Study CT-P43 3.1): The overall rates of SAEs were comparable across the treatment groups during TP1 and TP2. Infections and infestations were the most common System Organ Class (SOC) SAEs, and this is consistent with the known safety profile of ustekinumab products. All SAEs were singular events by Preferred Term (PT), with the exception of COVID-19 pneumonia in the CT-P43 treatment group during TP1 (n=2) (Table 21). Notably, Neoplasms SOC SAEs (n=2) and Gastrointestinal Disorders SOC SAEs (n=2) were reported only in the CT-P43 group. Other than the Neoplasms and Gastrointestinal Disorders SOC SAEs, there were no meaningful differences in the types and frequencies of SAEs between CT-P43 and EU-Stelara during the phase 3 development program.

Clinical Reviewer's Comment: Below, only the SAEs that are determined by the Investigator or by this reviewer to be possibly or likely related to CT-P43 are discussed in detail.

During TP1, one case of gastrointestinal inflammation SAE was reported for the CT-P43 group:

Subject (b) (6) was a 39-year-old white female. Her medical history included plaque psoriasis, appendectomy, appendicitis, benign breast lump removal, cholecystectomy, cholelithiasis, and tobacco poisoning. The subject had received CT-

P43 on Day 1 and Day 30. On Day 30, the subject was noted to have increases in serum triglyceride, aspartate transaminase (AST) and alanine transaminase (ALT) from the Baseline values. On Day 38 the participant experienced a Grade 3 SAE of gastrointestinal inflammation [Reported Term: other non-infectious gastroenteritis and colitis]. Adverse events that occurred within a +/- 3-day window of the onset of the SAE included hypertension (Grade grade 2), and uterine leiomyoma (Grade grade 1). Concomitant medications taken at the onset of the SAE included: drotaverine hydrochloride, enoxaparin sodium, ethinylestradiol;norelgestromin, nebivolol, and ramipril. The investigator considered the AE to be unrelated to study medication. The event ended on Day 41 with a final outcome of recovered/resolved.

Clinical Reviewer's Assessment: This reviewer's determination on the causality of the gastrointestinal inflammation is that it is likely related to the study drug. This determination is based on the fact that this SAE of GI inflammation occurred several days after the increase in the level of serum triglyceride, as well as liver transaminases, from Baseline, and hypertriglyceridemia is associated with GI and hepatic inflammation (Asekritova et al. 2015; Bruleu et al. 2014; Chen et al. 2023; Fu et al. 2022; Fujikawa et al. 2012; Kim et al. 2022; Mocanu et al. 2013; Moki et al. 2007; Park et al. 2008). Furthermore, the imbalance of these adverse events was observed in the CT-P43 treatment group.

During TP2, the following Gastrointestinal Disorders and Neoplasms SAEs were reported in the CT-P43 – CT-P43 treatment group: one case of acute pancreatitis, one case of colon adenoma, and one case of tubular adenocarcinoma of the breast:

- Acute pancreatitis: Subject (b) (6) was a 40-year-old white male. His medical history included plaque psoriasis, psoriatic arthritis, carpal tunnel syndrome, hyperlipidemia, hypertension, hyperuricemia, psoriatic arthropathy, spinal osteoarthritis, and type 2 diabetes mellitus. On Day 245, the participant experienced Grade 3 acute pancreatitis, which was considered a serious adverse event (SAE). Adverse events that occurred within a +/- 3-day window of the onset of the SAE included duodenitis (Grade 2), and hepatic steatosis (Grade 2). Concomitant medications taken at the onset of the SAE included: allopurinol, diclofenac sodium, insulin human injection, isophane, insulin lispro, lisinopril, and metformin hydrochloride. The investigator considered the AE to be unrelated to study medication. The event ended on Day 264 with a final outcome of recovered/resolved. Of note, at Screening and Baseline, his serum triglyceride level (TRIG) was reported at 11.44 mmol/L and 5.21 mmmol/L, respectively. His serum TRIG level increased (reached the limits of maximum detectable values of 50 mmmol/L on Day 80 and Day 85; 41.3 mmmol/L on Day 197) during the study before he experienced acute pancreatitis. His markedly increased serum triglyceride level from the Baseline was not documented as an AE.

Also of note in this case, the reported imaging studies demonstrated findings consistent with chronic pancreatitis. Other testing that supports likely chronic changes in the pancreas is that the elevation in amylase was lower than expected for an acute episode (less than 3X the upper limit of normal). The narrative also states that the subject had historically used fibrates, commonly used to treat hypertriglyceridemia, and that the treatment was not well tolerated.

Clinical Reviewer's Assessment: This reviewer's determination on the causality of the acute

pancreatitis is that it is likely related to the study drug. This determination is based on the fact that this SAE occurred in the setting of higher than the measurable limits of serum triglyceride levels that were markedly increased from his Baseline. Hypertriglyceridemia is a well-known cause of acute pancreatitis (Kiss et al. 2023). For this SAE, he was given treatment-emergent medications of ezetimibe, omega-3 fatty acids, and timonacic to treat hypertriglyceridemia, in addition to pantoprazole (no AE documented for pantoprazole). The subject may have had chronic pancreatitis prior to the study, but the worsening of his condition leading to an SAE of acute pancreatitis is likely due to CT-P43, given the imbalance of hypertriglyceridemia observed in the CT-P43 treatment group.

- Colon adenoma: Subject (b) (6) (also discussed leading in **6.3 Review of Safety Data, Safety Analyses and Data Integrity**)
- Colon adenoma: Subject (b) (6) (also discussed leading in 6.3 Review of Safety Data, Safety Analyses and Data Integrity) was a 41-year-old Asian male, and his medical history included plaque psoriasis. He had no prior history of systemic immunosuppressant use. On Day 1, he experienced “Grade 1 myalgia (abdomen)” and Grade 2 dyspepsia. The subject received FESTAL (ursodeoxycholic acid; cellulase ap; pancreatin; simethicone) for 3 days. The AEs were considered unrelated to the study medication and ended on Day 3 with a final outcome of recovered/resolved. On Day 233, a colon adenoma was reported, and it was considered an SAE and Grade 2 event. The lesion was found during a “pre-emptive health check-up” via endoscopy on Day 253, when the subject received cimetropium bromide, famotidine, ornithine aspartate, meperidine, flumazenil, midazolam, and propofol. The microscopic diagnosis from an endoscopic biopsy revealed a tubular adenoma. The investigator considered the AE to be unrelated to the study medication, and the event ended on Day 254 with a final outcome of recovered/resolved. On Day 302 the participant experienced acute hepatitis, a Grade 1 event. For the AE, the subject received GODEX (adenine hydrochloride; bifendate; carnitine orotate; cyanocobalamin; liver extract; pyridoxine hydrochloride; riboflavin). The investigator considered the AE to be unrelated to the study medication. Of note, the subject had increases in his serum triglyceride levels (as high as 6.29 mmol/L on Day 113) from his Screening (4.8 mmol/L) and Baseline (3.81 mmol/L) values during the study period.

Clinical Reviewer’s Assessment: The colon adenoma was classified as a Neoplasm SOC SAE and was said to be found during a “preemptive health check-up.” However, given his age of 41 years, his GI symptoms of dyspepsia and “myalgia (abdomen)” likely led to the subject’s 2-day hospitalization, when exploratory endoscopy that may have included upper, as well as lower endoscopy was performed to determine the cause for his GI symptoms. (He, at a later timepoint during the study, also had acute hepatitis.) Therefore, the TEAE of colon adenoma could be an incidental finding during the endoscopy. However, in addition to the immunosuppressive effect of the drug class for ustekinumab, the clinical comparability study showed that the CT-P43 – treated group had worsening features of metabolic syndrome, such as hypertriglyceridemia, hyperglycemia, and hypertension. Since metabolic syndrome is associated with increased risk of cancers (Zhan et al. 2024; Hsu et al. 2022; Kitayama et al. 2009; Ahmed et al. 2006; Mazumder et al. 2023; Esposito et al. 2012; Siddiqi et al. 2011), including formation of colon adenoma (Tabuchi et al. 2006) and its transition into colon cancer (Tabuchi et al. 2008), this reviewer’s determination on the causality is that it is possibly related to the study drug.

It is also notable that three subjects in the CT-P43 treatment group had Gastrointestinal SAEs.

- Tubular breast carcinoma: Subject (b) (6) was a 64-year-old white female in the CT-P43 – CT-P43 treatment group. Her medical history included plaque psoriasis, hypertension, seborrheic keratosis, and skin lesion. Her prior systemic immunosuppressant use included 13 months of adalimumab and 1 year of methotrexate, which were discontinued 269 days and 3 years, respectively, prior to starting CT-P43. On Day 295, 6 days after receiving her Week 40 dose, the subject reported the diagnosis of tubular breast adenocarcinoma [Reported Term: malignant tumor of the left breast], which was considered an SAE and Grade 3 event. Concomitant medications taken at the onset of the SAE included quinapril hydrochloride. The investigator considered the AE to be possibly related to the study medication. The subject underwent a breast quadrantectomy and radiotherapy and has been receiving hormone therapy. She is reported to be in remission.

Clinical Reviewer's Assessment: Because of the immunosuppressive effect of the drug class, this reviewer's determination on the causality is that it is possibly related to the study drug and concurs with the Investigator. Although metabolic syndrome is associated with breast cancer (Agresti et al. 2016; Dong et al. 2021; Rosato et al. 2011) and this subject had at Baseline hypercholesterolemia, increases in blood pressure, serum triglyceride or serum glucose levels from Baseline were not reported for this subject during the study.

Table 37 Treatment-Emergent Serious Adverse Events (SAEs), CT-P43 3.1 (Safety Set)

System Organ Class Preferred Term	EU-Stelara		CT-P43	
	TP1 (N=253) n (%)	TP2 (N=125) n (%)	TP1 (N=256) n (%)	TP2 (N=377) n (%)
Infections and infestations				
COVID-19 pneumonia	1 (0.4%)	1 (0.4%)	2 (0.8%)	0 (0.0%)
COVID-19	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
Tooth abscess	0 (0.0%)	0 (0.0)	0 (0.0%)	1 (0.3%)
Nervous system disorders				
Guillain-Barre syndrome	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
Subarachnoid haemorrhage	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders				
Gastrointestinal inflammation	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
Pancreatitis acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Respiratory, thoracic, and mediastinal disorders				
Respiratory failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Renal and urinary disorders				
Nephrolithiasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Cardiac disorders				
Myocardial infarction	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)

System Organ Class Preferred Term	EU-Stelara		CT-P43	
	TP1 (N=253) n (%)	TP2 (N=125) n (%)	TP1 (N=256) n (%)	TP2 (N=377) n (%)
Reproductive system and breast disorders				
Menstrual disorder	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neoplasms, benign, malignant, and unspecified				
Colon adenoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Tubular breast carcinoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Psychiatric disorders				
Bipolar disorder	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
Pregnancy, puerperium, and perinatal conditions				
Abortion spontaneous	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
All	4 (1.6%)	3 (2.4%)	4 (1.6%)	7 (1.9%)

Source: Clinical Reviewer

- Respiratory failure: Subject (b) (6) was a 44-year-old white male in the Switched to CT-P43 group, and his medical history included duodenal ulcer, plaque psoriasis, psoriatic arthritis, gastroesophageal reflux disease, gilbert's syndrome, head injury, hypercholesterolaemia, intervertebral disc disorder, intracranial haematoma, psoriatic arthropathy, and spinal osteoarthritis. His concomitant medications included meloxicam and phospholipid soybean.

On Day 84 during TP1 on EU-Stelara, the subject experienced a Grade 3 SAE of subarachnoid haemorrhage. On Day 113 during TP2 on CT-P43, a TEAE of a venous angioma of brain [developmental venous anomalies - left temporal lobe none additional information] (Grade 1) was recorded. On Days 113 and 197 he experienced a gamma-glutamyltransferase increased [ggt increase] (Grade 1).

On Day 228 it was reported that he experienced a Grade 2 TEAE of "pneumonia viral", and he received cefuroxime, clarithromycin, fenoterol hydrobromide: ipratropium bromide, hydrocortisone, inosine pranobex, metamizole, and althea officinalis. The AE narrative stated that the AE ended on Day 248 with a final outcome of recovered/resolved. However, on Day 249 he was hospitalized with a Grade 3 SAE of respiratory failure. The chest x-ray, CT scan, and high resolution CT scan showed no evidence of pneumonia ("no signs of pulmonary embolism, pulmonary parenchyma without densities, no evidence of fluid in the pleural cavities, mediastinal structures, large vessels of the chest were normal, no enlargement of the lymph nodes of the pulmonary hila and mediastinum were found, and on the borderline of the test scope, there was an increased steatosis in the liver parenchyma"). The subject was given TEAE medications of fenofibrate for hypertriglyceridemia (Grade 2), nebivolol and zofenopril for hypertension (Grade 2), metformin for glucose tolerance impaired (Grade 1). Arrhythmia supraventricular (Grade 2) and myocardial ischaemia (Grade 2) were also reported. He was also started on fluticasone propionate:salmeterol xinafoate, ciclesonide, and salbutamol for asthma (Grade 2) and discharged from the hospital on Day 257. The action taken with the study drug was drug withdrawn.

Clinical Reviewer's Comment: The Applicant assessed the respiratory failure as possibly related to the study drug, citing that the "onset of date is one day after resolution of another adverse event of viral pneumonia." This reviewer's determination on causality for the SAE of respiratory

failure is that it's likely related to CT-P43. However, this reviewer disagrees with the Applicant that the respiratory failure is due to viral pneumonia, because the subject's radiographic and laboratory results do not support that he had pneumonia. Even though the subject's "SatO2 was 90% in pulse oximeter serial measurements and the diagnosis was suspected interstitial disease," the high-resolution computed tomography (HRCT) of the chest and arterial blood were negative for pneumonia, pleural effusion, any pathology in the lung parenchyma, or interstitial disease. It did show steatohepatosis.

He also recovered after receiving an inhaled corticosteroid and bronchodilator for asthma, in addition to starting fenofibrate for hypertriglyceridemia, metformin for hyperglycemia, and nebivolol and zofenopril for hypertension. He was experiencing concomitant arrhythmia and myocardial ischaemia. It is well known that metabolic syndrome is associated with asthma or dyspnea, and the patient's newly diagnosed asthma may be yet another example that metabolic syndrome was worsening in some of the subjects treated with CT-P43.

Treatment Emergent Adverse Events

Healthy Volunteers: In Study CT-P43 1.1, 86% of participants in CT-P43 group experienced at least 1 TEAE, compared to 82% in the US-Stelara group and 78% in the EU-Stelara group (Table 30). In Study CT-P43 1.2, 55% of participants in CT-P43 group experienced at least 1 TEAE, compared to 45% in the US-Stelara group and 50% in the EU-Stelara group (Table 58). While AEs were generally comparable across the treatment groups, it is notable that AEs related to the General Disorders and Administration Site Conditions SOC were more frequent in the CT-P43 group, compared to the US-Stelara and EU-Stelara groups. More specifically, in Study CT-P43 1.2, the repeat pharmacokinetic study that met the comparability criteria, injection site reactions were notably more common in the CT-P43-group (20%), compared to the US-Stelara (9%) and EU-Stelara (13%) groups. In Study CT-P43 1.1, in which the pharmacokinetic study failed, injection site reactions were reported in 12% in the CT-P43 group, compared to 9% in the US-Stelara group and 10% in the EU-Stelara group. The injection site reactions are discussed in more detail in **Adverse Events of Special Interest** under *Injection Site Reactions*. Otherwise, no particular pattern emerged from the rates of individual AEs across the treatment groups in the two single-dose PK studies with healthy volunteers (Table 57 and Table 58).

Table 38 Treatment-Emergent Adverse Events for $\geq 1\%$, CT-P43 3.1 (Safety Analysis Set)

Body System or Organ Class Dictionary-Derived Term	TP1		TP2		
	CT-P43 (n=256)	EU- Stelara (n=253)	CT-P43- CT-P43 (n=256)	EU- Stelara- CT-P43 (n=)	EU- Stelara- EU- Stelara (n=125)
Infections and infestations					
COVID-19	11 (4.3%)	12 (4.7%)	13 (5.1%)	7 (5.6%)	11 (8.8%)
Upper respiratory tract infection	3 (1.2%)	8 (3.2%)	10 (4.0%)	7 (5.6%)	4 (3.2%)
Latent tuberculosis	0 (0%)	0 (0%)	7 (2.8%)	4 (3.2%)	4 (3.2%)
Nasopharyngitis	2 (0.8%)	1 (0.4%)	1 (0.4%)	4 (3.2%)	1 (0.8%)
Oral herpes	1 (0.4%)	3 (1.2%)	0 (0%)	0 (0%)	0 (0%)
Sinusitis	3 (1.2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)

Body System or Organ Class Dictionary-Derived Term	TP1		TP2		
	CT-P43 (n=256)	EU- Stelara (n=253)	CT-P43- CT-P43 (n=256)	EU- Stelara- CT-P43 (n=)	EU- Stelara- EU- Stelara (n=125)
Investigations					
Alanine aminotransferase increased	5 (2.0%)	4 (1.6%)	3 (1.2%)	6 (4.8%)	3 (2.4%)
Gamma-glutamyltransferase increased	3 (1.2%)	2 (0.8%)	5 (2.0%)	3 (2.4%)	1 (0.8%)
Aspartate aminotransferase increased	3 (1.2%)	0 (0%)	2 (0.8%)	4 (3.2%)	3 (2.4%)
White blood cell count decreased	1 (0.4%)	1 (0.4%)	4 (1.6%)	3 (2.4%)	3 (2.4%)
Blood creatine phosphokinase increased	2 (0.8%)	4 (1.6%)	2 (0.8%)	0 (0%)	2 (1.6%)
Neutrophil count decreased	0 (0%)	1 (0.4%)	1 (0.4%)	3 (2.4%)	2 (1.6%)
General disorders and administration site conditions					
Vaccination site pain	5 (2.0%)	6 (2.4%)	3 (1.2%)	0 (0%)	2 (1.6%)
Injection site reaction	3 (1.2%)	2 (0.8%)	1 (0.4%)	2 (1.6%)	0 (0%)
Pyrexia	3 (1.2%)	1 (0.4%)	1 (0.4%)	0 (0%)	2 (1.6%)
Metabolism and nutrition disorders					
Hypertriglyceridemia	4 (1.6%)	2 (0.8%)	4 (1.6%)	4 (3.2%)	1 (0.8%)
Musculoskeletal and connective tissue disorders					
Psoriatic arthropathy	4 (1.6%)	2 (0.8%)	0 (0%)	0 (0%)	2 (1.6%)
Back pain	1 (0.4%)	3 (1.2%)	0 (0%)	0 (0%)	1 (0.8%)
Myalgia	3 (1.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nervous system disorders					
Headache/Migraine	7 (2.7%)	4 (1.6%)	5 (2%)	1 (0.8%)	1 (0.8%)
Dizziness	3 (1.2%)	1 (0.4%)	1 (0.4%)	0 (0%)	0 (0%)
Ear/Labyrinthine disorders					
Vertigo/Positional vertigo/Dizziness/Balance disorder	3 (1.2%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)
Blood and lymphatic system disorders					
Neutropenia	4 (1.6%)	4 (1.6%)	0 (0%)	2 (1.6%)	2 (1.6%)
Vascular disorders					
Hypertension	7 (2.7%)	1 (0.4%)	2 (0.8%)	2 (1.6%)	2 (1.6%)

Source: Clinical Reviewer

Table 39 Treatment-Emergent Adverse Events (Grade 3 or higher) in Study CT-P43 3.1

Body System or Organ Class Dictionary-Derived Term	TP1		TP2		
	CT-P43	EU-Stelara	CT-P43- CT-P43	EU-Stelara- CT-P43	EU-Stelara- EU-Stelara
Infections and infestations					
Latent tuberculosis	0	0	2 (0.8%)	0	0
COVID-19 pneumonia	2 (0.8%)	1 (0.4%)	0	0	1 (0.8%)
Tooth abscess	0	0	1 (0.4%)	0	0
Investigations					
Alanine aminotransferase increased	0	0	0	1 (0.8%)	0
Gamma-glutamyltransferase increased	0	1 (0.4%)	0	0	0

Body System or Organ Class Dictionary-Derived Term	TP1		TP2		
	CT-P43	EU-Stelara	CT-P43- CT-P43	EU-Stelara- CT-P43	EU-Stelara- EU-Stelara
Aspartate aminotransferase increased	0	0	0	1 (0.8%)	0
White blood cell count decreased	0	1 (0.4%)	0	1 (0.8%)	0
Blood creatine phosphokinase increased	1 (0.4%)	0	0	0	0
Neutrophil count decreased	0	1 (0.4%)	0	2 (1.6%)	2 (1.6%)
Blood triglycerides increased	0	1 (0.4%)	0	1 (0.8%)	0
Blood cholesterol increased	0	1 (0.4%)	0	0	0
Blood potassium decreased	0	0	0	1 (0.8%)	0
Muscle enzyme increased	1 (0.4%)	0	0	0	0
Metabolism and nutrition disorders					
Hypertriglyceridaemia	3 (1.2%)	2 (0.8%)	2	0	1 (0.8%)
Nervous system disorders					
Headache	2 (0.8%)	0	2 (0.8%)	0	0
Guillain-Barre syndrome	0	0	0	0	1 (0.8%)
Subarachnoid haemorrhage	0	1 (0.4%)	0	0	0
Gastrointestinal disorders					
Gastrointestinal inflammation	1 (0.4%)	0	0	0	0
Pancreatitis acute	0	0	1 (0.4%)	0	0
Blood and lymphatic system disorders					
Neutropenia	4 (1.6%)	4 (1.6%)	0	1 (0.8%)	2 (1.6%)
Leukopenia	0	0	1 (0.4%)	0	0
Injury, poisoning and procedural complications					
Ligament sprain	0	1 (0.4%)	0	0	0
Respiratory, thoracic and mediastinal disorders					
Respiratory failure	0	0	0	1 (0.8%)	0
Renal and urinary disorders					
Nephrolithiasis	0	0	0	1 (0.8%)	0
Cardiac disorders					
Myocardial infarction	0	0	1 (0.4%)	0	0
Reproductive system and breast disorders					
Menstrual disorder	0	1 (0.8%)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Tubular breast carcinoma	0	0	1 (0.4%)	0	0
Psychiatric disorders					
Bipolar disorder	1 (0.8%)	0	0	0	0
Immune system disorders					
"Hypersensitivity"	0	0	1 (0.4%)	0	0
Pregnancy, puerperium and perinatal conditions					
Abortion spontaneous	0	1 (0.8%)	0	0	0

Source: Clinical Reviewer

Subjects with PsO (Study CT-P43 3.1) during TP1: The comparative safety of CT-P43 relative to EU-Stelara relies partly on the data from the TP1 of CT-P43 3.1, where subjects with PsO were exposed to either product for up to 16 weeks. The overall incidence rates of TEAEs were 155 events in 95 (37.1%) subjects in the CT-P43 group and 108 events in 75 (29.6%) subjects

in the EU-Stelara group (Table 38). The majority of TEAEs during TP1 were Grade 1 or 2 in severity. There were 21 Grade 3 events (12 [4.7%] subjects in the CT-P43 group and 9 [3.6%] subjects in the EU-Stelara group) and 7 Grade 4 events (3 [1.2%] subjects in the CT-P43 group and 4 [1.6%] subjects in the EU-Stelara group) (Table 39). Most Grade 3 or higher AEs were singular events or occurred at low rates during TP1. The SOC with the highest percentage of subjects reporting TEAEs of all causalities were Infections and Infestations SOC in both treatment groups with similar incidence rates; there were 39 AEs in 34 (13.3%) subjects in the CT-P43 group and 35 AEs in 32 (12.6%) subjects in the EU-Stelara group with the most commonly reported preferred terms (PTs) being COVID-19 and upper respiratory tract infection.

During TP1, several imbalances were seen with the following SOC or PT AEs: Gastrointestinal Disorders, Metabolism and Nutrition Disorders, hypertriglyceridemia, headache or migraine, and hypertension. These imbalances are discussed in detail.

Gastrointestinal (GI) SOC AEs were seen at a slightly higher rate in the CT-P43 group (10 AEs in 7 subjects (2.7%)) than in the EU-Stelara group (3 AEs in 3 subjects (1.2%)) (Table 40). Including Helicobacter infection PT in the GI Disorders SOC would change this to 8 subjects (3.1%) in the CT-P43 group and 3 subjects (1.2%) in the EU-Stelara group. Although each PT AE occurred at low rates, many of the PT AEs in the CT-P43 group, such as abdominal (epigastric) hernia, hiatal hernia, gastric ulcer, dyspepsia, gastritis, and upper abdominal pain are associated with upper gastrointestinal inflammation. Furthermore, three of these subjects in the CT-P43 group were started on proton-pump inhibitors (PPIs) during TP1, whereas no subject with Gastrointestinal Disorders SOC AEs in the EU-Stelara group was started on a PPI.

Table 40 Gastrointestinal Disorders SOC AEs during TP1, CT-P43 3.1 (Safety Analysis Set)

System Organ Class Preferred Term	CT-P43 N=256 n (%)	EU-Stelara N=253 n (%)	Risk Difference		
			RD	(95% CI)	Forest Plot
Gastrointestinal disorders	7 (2.7)	3 (1.2)	1.55	(-0.85, 3.95)	
Abdominal hernia	1 (0.4)	0 (0.0)	0.39	(-0.37, 1.15)	
Abdominal pain	0 (0.0)	1 (0.4)	-0.40	(-1.17, 0.38)	
Abdominal pain upper	2 (0.8)	0 (0.0)	0.78	(-0.30, 1.86)	
Constipation	1 (0.4)	0 (0.0)	0.39	(-0.37, 1.15)	
Diarrhoea	0 (0.0)	1 (0.4)	-0.40	(-1.17, 0.38)	
Dyspepsia	1 (0.4)	0 (0.0)	0.39	(-0.37, 1.15)	
Gastric ulcer	1 (0.4)	0 (0.0)	0.39	(-0.37, 1.15)	

Gastritis	1 (0.4)	0 (0.0)	0.39	(-0.37, 1.15)	
Gastrointestinal inflammation	1 (0.4)	0 (0.0)	0.39	(-0.37, 1.15)	
Hiatus hernia	1 (0.4)	0 (0.0)	0.39	(-0.37, 1.15)	
Nausea	0 (0.0)	1 (0.4)	-0.40	(-1.17, 0.38)	
Stomatitis	1 (0.4)	0 (0.0)	0.39	(-0.37, 1.15)	

Source: Clinical Reviewer

There was an imbalance (Table 25) in the Metabolisms and Nutrition Disorders SOC AEs, with more AEs occurring in the CT-P43 group (12 subjects (4.7%)), compared to the EU-Stelara group (4 subjects (1.6%)). The following PT AEs were included, with hypertriglyceridemia being the most common: hypercholesterolemia, obesity, dyslipidemia, hyperlipidemia, lipid metabolism disorder, hyperglycaemia, insulin resistance, and hyperuricaemia. Hyperglycaemia PT and insulin resistance PT occurred in 3 subjects (1.2%) in the CT-P43 group and 0 subjects in the EU-Stelara group.

During TP1, 7 (2.7%) subjects in the CT-P43 group and 1 (0.4%) subject in the EU-Stelara group had hypertension PT AEs, and all of these subjects were started on antihypertensive agents, suggesting that these hypertensive episodes were notable and persistent.

During TP1, 7 (2.7%) subjects in the CT-P43 group and 4 (1.6%) subjects in the EU-Stelara group had headache or migraine (Table 38). There were two subjects PTs in the CT-P43 group (0 subject in the EU-Stelara group) that experienced Grade 3 headaches, and both subjects (also discussed in **6.3 Review of Safety Data, Safety Analyses and Data Integrity**) eventually withdrew from the study because of this AE. In summary, there was an imbalance in the number of subjects that experienced headache or migraine PT, as well as in the intensity of the headache PTs.

During TP1, 3 (1.2%) subjects in the CT-P43 group and 1 (0.4%) subject in the EU-Stelara group had dizziness or vertigo (Table 38). Of note, Subject (b) (6) in the CT-P43 group started betahistine hydrochloride for dizziness, but was not documented to have dizziness as an AE. One subject in the CT-P43 group experienced the onset of hypertension and vertigo at the same time and continued to experience multiple episodes of dizziness, which was still ongoing at the end of the study. His narrative is briefly summarized:

Subject (b) (6) was a 58-year-old white male, whose medical history included plaque psoriasis, hypertension, and osteoarthritis. On Day 33, he experienced a Grade 2 TEAE of worsening hypertension, for which he started amlodipine; ramipril, sublingual captopril, and nitrendipine and a Grade 2 TEAE of vertigo positional (final outcome of recovered), for which he was given betahistine hydrochloride and metoclopramide hydrochloride. On Day 93 he experienced a Grade 2 TEAE of vertigo (final outcome of recovered). On the same day, his amlodipine; ramipril for hypertension was switched to hydrochlorothiazide; valsartan, and on Day 94 piracetam and vinpocetine were started for the dizziness, in addition to betahistine hydrochloride. On Day 143 he experienced a Grade 2 TEAE of balance disorder (final outcome of not

recovered) and on Day 186 he experienced a Grade 1 TEAE of dizziness (final outcome of recovered).

The only Hepatobiliary SOC AE, non-alcoholic fatty liver disease (NAFLD), was seen in 1 subject (0.4%) in the CT-P43 group and in 0 subjects in the EU-Stelara group. The NAFLD subject was started on phospholipid soybean, which is used for lowering blood levels of triglyceride and cholesterol, and timonacic, which is used to treat hepatic disorders, including fatty liver disease. Notably, during TP1 in the CT-P43 group 5 subjects (2.0%) started various medications (ursodeoxycholic acid, GODEX, timonacic, phospholipid soybean, and/or silybum marianum) in the Bile and Liver Injury Class: (b) (6)

These subjects had one or more of these AEs: nonalcoholic fatty liver disease, dyslipidemia, hyperlipidemia, gamma-glutamyl transferase increased, alanine transaminase increased, and aspartate transaminase increased. No subject in the EU-Stelara group reported NAFLD or started a medication in the Bile and Liver Injury Class during TP1.

Clinical Reviewer's Summary of TP1: During TP1, increased blood pressure or worsening of hypertension occurred predominantly in the CT-P43 group, and the risk difference was notable. All these subjects were started on long-term anti-hypertensives for this TEAE. Additionally, more cases of headache and dizziness were observed in the CT-P43 group, compared to the EU-Stelara group, and Grade 3 headaches occurred only in the CT-P43 group, and for one of the 2 subjects these severe headache episodes were later reported to coincide with marked increases in systolic blood pressure. For one of the 3 subjects with dizziness in the CT-P43 group, the onset coincided with worsening of hypertension, and it was later reported that the dizziness was significant and persistent. Taken together, worsening of hypertension, sometimes associated with concomitant headache or dizziness, seen in the CT-P43 group appears to be clinically meaningful.

The other notable risk difference was observed in the Metabolism and Nutrition Disorders SOC. Most TEAEs involved hyperlipidemia (hypertriglyceridemia, in particular) or hyperglycemia; AEs involving hyperglycemia were only observed in the CT-P43 group. The imbalances seen in the TEAEs with Gastrointestinal Disorders SOC (especially the ones involving upper GI inflammation) and Hepatobiliary Disorders SOC were notable, especially in that many of those subjects in the CT-P43 group had increases in the serum triglyceride levels from their Baseline during the study. Moreover, subjects with Gastrointestinal SOC TEAEs in the CT-P43 group only and not in the EU-Stelara group were started on proton pump inhibitors or medications often given for fatty liver disease during TP1.

Of note, multiple reports have associated hypertriglyceridemia with symptoms of gastroesophageal reflux disease (GERD), hepatic steatosis, and pancreatitis (Kim et al. 2022; Fujikawa et al. 2012; Chen et al. 2023; Fu et al. 2022; Bruley des Varannes et al. 2014; Mocanu et al. 2013; Asekritova et al. 2015; Park et al. 2008; Moki et al. 2007; Sahu et al. 2020; Werlabg et al. 2017; Gunawan et al. 2019; Interleukin Inhibitors and the risk of pancreatitis. 2023). Taken together, this imbalance in Metabolism and Nutrition Disorders SOC appears to be clinically meaningful.

Table 41 Treatment Emergent Adverse Event (TEAE) imbalances during Treatment Period 1 (TP1)

System Organ Class	CT-P43	Risk Difference
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Preferred Term	N=256 n (%)	EU- Stelara N=253 n (%)	RD	(95% CI)	Forest Plot
Gastrointestinal disorders	7 (2.7)	3 (1.2)	1.55	(-0.85, 3.95)	
Metabolism and nutrition disorders	12 (4.7)	1 (0.4)	3.11	(0.19, 6.12)	
Headache/Migraine	7 (2.7)	4 (1.6)	1.15	(-1.37, 3.67)	
Hypertension/BP increased	7 (2.7)	1 (0.4)	2.34	(0.20, 4.48)	

Source: Clinical Reviewer

Subjects with PSO (Study CT-P43 3.1) during TP2: The design of the second part of Study CT-P43 3.1 allows for an assessment of safety that compares continuous treatment to that of switching products. Overall, 326 TEAEs were reported in 189 (37.6%) subjects (86 [34.0%], 51 [40.8%], and 52 [41.9%] subjects in the CT-P43 maintenance, Switched to CT-P43, and EU-Stelara maintenance groups, respectively) (Table 38). The majority of TEAEs during TP2 were mild or moderate in severity (Grade 1 or 2). The rates of Grade 3 or higher TEAEs were low, and the majority of them were singular events, but the highest incidence rate was observed in the switching arm, compared to the non-switching arms (Table 39). There were 23 Grade 3 events (10 [4.0%], 6 [4.8%], and 7 [5.6%] subjects in the CT-P43 maintenance, EU-Stelara maintenance, and Switched to CTP43 groups, respectively), 3 Grade 4 events (0 [0%], 1 [0.8%], and 2 [1.6%] subjects in the CT-P43 maintenance, EU-Stelara maintenance, and Switched to CT-P43 groups, respectively), and 1 Grade 5 (death) event in the CT-P43 maintenance group.

During TP2, the Gastrointestinal SOC AEs were seen at higher rates in the CT-P43 group (10 AEs in 9 subjects (2.4%)) than in the EU-Stelara group (1 AE in 1 subject (0.8%)). These Gastrointestinal SOC AEs are shown in the table below (Table 42). Although each GI AE occurred at a low rate, some of the GI AEs, such as duodenitis and gastroesophageal reflux disease, occurred only in the CT-P43 group and are clinically associated with upper gastrointestinal inflammation. Notably, similar to TP1, 3 of these subjects in the CT-P43 group were started on PPIs, whereas no subject with the GI Disorders SOC AE in the EU-Stelara group was started on a PPI.

The Hepatobiliary SOC AEs were reported in 6 (1.6%) subjects for the CT-P43 group and in 0 subjects in the EU-Stelara group (Table 38). Four of the 6 subjects reported hepatic steatosis, nonalcoholic fatty liver disease, or nonalcoholic steatohepatitis. Subject (b) (6) who reported hepatitis acute (as discussed in **Quality and Integrity of Safety Data**) had increases in his serum triglyceride level from his Baseline during the study.

Hypertriglyceridemia or blood triglyceride increased PT was reported in 9 (2.4%) subjects in the CT-P43 group and in 1 subject (1.6%) in the EU-Stelara group. Of note, some subjects with abnormal blood triglyceride levels higher than the Baseline values were not documented to have hypertriglyceridemia PT AEs. Therefore, the reported number for hypertriglyceridemia PT AEs underrepresent the actual incidence rate.

An imbalance was also seen with Respiratory Disorders SOC with all AEs occurring in the CT-P43 group. One subject was treated for chronic obstructive pulmonary disease (not included in medical history at Screening), and one subject was treated for asthma (not included in medical

history at Screening) and respiratory failure PT SAE requiring hospitalization (discussed in Serious Adverse Events).

Table 42 Treatment Emergent Adverse Event (TEAE) imbalances during Treatment Period 2 (TP2)

Summary of TEAEs - Group Terms

Group Term Preferred Term	CT-P43 N = 377	Stelara N = 129	Risk Difference	
	n (%)	n (%)	RD (95% CI)	Forest Plot
Hyperlipidemia	10 (2.6)	1 (0.8)	1.86 (-0.35, 4.07)	
Hypercholesterolaemia	2 (0.5)	0 (0.0)	0.53 (-0.20, 1.25)	
Hyperglycaemia	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Hyperlipidaemia	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Hypertriglyceridaemia	8 (2.1)	1 (0.8)	1.33 (-0.76, 3.42)	
Gastrointestinal disorders	9 (2.4)	1 (0.8)	1.59 (-0.56, 3.74)	
Abdominal pain	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Dental pulp disorder	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Diarrhoea	2 (0.5)	0 (0.0)	0.53 (-0.20, 1.25)	
Duodenitis	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Food poisoning	2 (0.5)	0 (0.0)	0.53 (-0.20, 1.25)	
Gastrointestinal disorder	0 (0.0)	1 (0.8)	-0.78 (-2.29, 0.74)	
Gastrooesophageal reflux disease	2 (0.5)	0 (0.0)	0.53 (-0.20, 1.25)	
Pancreatitis acute	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Headache	7 (1.8)	1 (0.8)	1.07 (-0.96, 3.10)	
Headache	6 (1.6)	1 (0.8)	0.80 (-1.16, 2.77)	
"Hypersensitivity"	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	

Summary of TEAEs - Group Terms

Group Term Preferred Term	CT-P43 N = 377	Stelara N = 129	Risk Difference	
	n (%)	n (%)	RD (95% CI)	Forest Plot
Hepatic steatosis	4 (1.1)	0 (0.0)	1.05 (0.03, 2.08)	
Hepatic steatosis	2 (0.5)	0 (0.0)	0.53 (-0.20, 1.25)	
Non-alcoholic steatohepatitis	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Nonalcoholic fatty liver disease	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Hepatobiliary Disorder	6 (1.6)	0 (0.0)	1.58 (0.33, 2.83)	
Hepatic cirrhosis	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Hepatic steatosis	2 (0.5)	0 (0.0)	0.53 (-0.20, 1.25)	
Hepatitis acute	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Non-alcoholic steatohepatitis	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Nonalcoholic fatty liver disease	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Hyperglycaemia	3 (0.8)	0 (0.0)	0.79 (-0.10, 1.68)	
Diabetes mellitus	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Glucose tolerance impaired	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Hyperglycaemia	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Injection Site Reaction	3 (0.8)	0 (0.0)	0.79 (-0.10, 1.68)	
Injection site reaction	3 (0.8)	0 (0.0)	0.79 (-0.10, 1.68)	
Neoplasms	6 (1.6)	0 (0.0)	1.58 (0.33, 2.83)	
Adrenal neoplasm	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Breast mass	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Goitre	2 (0.5)	0 (0.0)	0.53 (-0.20, 1.25)	

Summary of TEAEs - Group Terms

Group Term Preferred Term	CT-P43 N = 377	Stelara N = 129	Risk Difference	
	n (%)	n (%)	RD (95% CI)	Forest Plot
Neoplasm	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Prostatic mass	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Tubular breast carcinoma	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Respiratory Disorders	7 (1.8)	0 (0.0)	1.84 (0.49, 3.19)	
Asthma	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Chronic obstructive pulmonary disease	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Cough	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Oropharyngeal pain	2 (0.5)	0 (0.0)	0.53 (-0.20, 1.25)	
Pharyngeal inflammation	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Respiratory failure	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	
Rhinorrhoea	1 (0.3)	0 (0.0)	0.26 (-0.25, 0.78)	

Source: Clinical Reviewer OCS Analysis Studio, Safety Explorer.

Filters: ACTARM = "CT-P43 (Treatment1" or "CT-P43 (Treatment1-CT-P43 (Treatment2" or "Stelara (Treatment1-CT-P43 (Treatment2" and SAFFL = "Y" (CT-P43); ACTARM = "Stelara (Treatment1-Stelara (Treatment2" or "Stelara (Treatment1" and SAFFL = "Y" (Stelara); TRTEMFL = "Y" and APERIODC = "PERIOD 02" (Adverse Events).

Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Please be aware that the following PTs are present in multiple Group Terms: "Hepatic steatosis", "Hyperglycaemia", "Non-alcoholic steatohepatitis", "Nonalcoholic fatty liver disease".

Neoplasms (malignant, benign, or undefined) during Treatment Period 1 and Treatment Period 2

Although benign, malignant, and unspecified neoplasms were rare in Study CT-P43 3.1, all the cases occurred while receiving CT-P43, and most cases (eight out of ten lesions) occurred during TP2.

One TEAE related to malignancy, tubular breast carcinoma, was reported in subject (b) (6) in the CT-P43 maintenance group during TP2. This subject is discussed in more detail above under **Serious Adverse Events**.

For benign or undefined neoplasms, eight additional subjects reported AEs (Table 43). These cases are discussed in more detail below:

- 1) Breast mass: Subject (b) (6) was a 55-year-old White female in the Switched to CT-P43 group, and her medical history included appendicitis, appendectomy, peritonitis and laparotomy, ischaemic stroke and hemiparesis, supraventricular arrhythmia, and sciatica. The subject's ongoing medical conditions

included talipes, obesity, hypertension, psoriatic arthropathy, spinal osteoarthritis, impaired glucose tolerance, arteriosclerosis, hyperuricemia, intervertebral disc disorder, and dry eye. Her prior systemic immunosuppressant use included 3.8 years of methotrexate and 18 days of methylprednisolone, which were discontinued 40 days and 33 days, respectively, prior to starting CT-P43. Concomitant medications for indications other than adverse events included acetylsalicylic acid and ramipril. On Day 360, 56 days after the Week 40 dose, the subject experienced a Grade 2 TEAEs of a “left nipple lump.” The Applicant stated that further information about the malignancy or final diagnosis was not available, and the AE was considered to be not resolved at the time of final database lock. Other reported TEAEs included swelling of the left shin and left foot trauma during TP1 and latent tuberculosis, upper respiratory tract infection, and rib fracture during TP2. The subject completed the trial.

- 2) Prostatic mass: Subject (b) (6) was a 72-year-old white male in the CT-P43 maintenance group, and his medical history included plaque psoriasis, aortic aneurysm, benign prostatic hyperplasia, hypertension, myopia, osteoarthritis, peptic ulcer, prostatic operation, and spinal osteoarthritis. On Day 276 (79 days after Week 28 dose), the subject experienced a Grade 2 TEAE of “nodular lesions with decreased signal – prostate gland.” His previous use of immunosuppressive medications included 3.7 months of adalimumab, which was discontinued 122 days prior to starting CT-P43. Concomitant medications taken at the onset of the AE included: acetylsalicylic acid, allopurinol, cetomacrogol 1000; cetostearyl alcohol; paraffin, liquid; petrolatum; phenoxyethanol, chondroitin sulfate sodium, finasteride, indapamide, magnesium lactate; pyridoxine hydrochloride, potassium chloride, quinapril hydrochloride, and tamsulosin hydrochloride. The study drug was withdrawn because of the AE. Per the Applicant, to date, the diagnosis is not confirmed. His other AEs included enlarged inguinal lymphadenopathy, focal lesion of the right femur, hyperuricemia, bilateral narrowing of hip joints, and osteoarthritis during TP2. Per the Investigator, the right femur lesion is a benign cyst, and the enlarged inguinal lymphadenopathy has resolved as of March 2022.
- 3) Cervical dysplasia: Subject (b) (6) was a 64-year-old Asian female in the CT-P43 maintenance group, and her medical history included glaucoma, infective keratitis, ulcerative keratitis, plaque psoriasis, blindness unilateral, diabetes mellitus, hepatic steatosis, hyperlipidaemia, hypertension, and thyroid neoplasm. She had no prior history of systemic immunosuppressant use. On Day 84 (Week 12 visit date), she experienced a Grade 2 TEAE of “cervical intraepithelial neoplasia,” which was mapped to “cervical dysplasia” by the Applicant. Concomitant medications taken at the onset of the AE included: GODEX (adenine hydrochloride; bifendate; carnitine orotate; cyanocobalamin; liver extract; pyridoxine hydrochloride; riboflavin, brimonidine tartrate; timolol maleate, brinzolamide, lercanidipine hydrochloride; valsartan, levothyroxine sodium, metformin hydrochloride; teneligliptin hydrobromide, proxymetacaine hydrochloride, rosuvastatin calcium, and vitis vinifera extract. The subject underwent loop electrosurgical excision procedure and treatment medications for the AE. The information about whether the lesion was benign or malignant was not available, and the Investigator confirmed that the event is still ongoing in (b) (6). Other TEAEs included myalgia and glycosuria during TP1 and bacterial keratitis, glycosuria, and hyperglycemia during TP2. The subject completed the trial.
- 4) Lung tumor/adrenal neoplasm: Participant (b) (6) was a 31-year-old white male in the CT-P43 maintenance group, and his medical history included plaque

psoriasis and ligament sprain. He had no prior history of systemic immunosuppressant use. On Day 294 (93 days after Week 28 dose), he experienced a Grade 1 TEAE of “solid left lung tumor” and Grade 1 TEAE of “right adrenal tumor – abnormal result detected in the HRCT of chest.” Adverse events that occurred within a +/- 3-day window of the onset of the AE included non-alcoholic steatohepatitis (Grade 1). Concomitant medications taken at the onset of the AE included: butyl hydroxybenzoate; cetyl alcohol; propylene glycol; sodium lauryl sulfate; stearyl alcohol; water purified, and cetyl alcohol; propylene glycol; sodium lauryl sulfate; stearyl alcohol. As of (b) (6) the Investigator stated that whether the lung or adrenal lesions are benign or malignant are unknown and that additional diagnostic test results were not available. Other TEAEs included hypertriglyceridemia and erythema of the right axillary region during TP1 and COVID-19 infection, hypertriglyceridemia, and non-alcoholic steatohepatitis during TP2. The subject completed the trial.

- 5) Colon adenoma: This is discussed in more detail under **Serious Adverse Events** in **7.3.2**.
- 6) Uterine leiomyoma: Participant (b) (6) was a 39-year-old white female in the CT-P43 maintenance group, and her medical history included plaque psoriasis, appendectomy, appendicitis, benign breast lump removal, cholecystectomy, cholelithiasis, and tobacco poisoning. Her prior systemic immunosuppressant use included 2 years of methotrexate, which was discontinued 4 years prior to starting CT-P43. On Day 40 (10 days after Week 4 dose), she experienced a Grade 1 TEAE of “uterine myomas.” Adverse events that occurred within a +/- 3-day window of the onset of Grade 3 TEAE of gastrointestinal inflammation. Concomitant medications taken at the onset of the AE included: drotaverine hydrochloride, enoxaparin sodium, ethinylestradiol; norelgestromin, nebivolol, and ramipril. It had a final outcome of not recovered/not resolved. Other TEAEs included COVID-19 infection, hypertension, gastrointestinal inflammation, gastritis, Helicobacter infection, and hiatal hernia during TP1. The subject completed the trial.
- 7) Goiter: Participant (b) (6) was a 64-year-old white male in the Switched to CT-P43 treatment group, and his medical history included renal cyst, erosive duodenitis, polypectomy, rectal polyp, varicose vein, arteriosclerosis, coronary angioplasty, coronary angioplasty, hepatic steatosis, hyperlipidaemia, type 2 diabetes mellitus, plaque psoriasis, adrenal adenoma, coronary artery disease, hypertension, and obesity. He had no prior history of systemic immunosuppressant use. On Day 154 (68 days after the Week 28 dose) he experienced a Grade 1 TEAE of “goiter.” Concomitant medications taken at the onset of the AE included: acetylsalicylic acid, amlodipine besilate, empagliflozin, metformin hydrochloride, ramipril, rosuvastatin calcium, ticagrelor, and torasemide. Other TEAEs included a renal cyst during TP1. The subject completed the trial. As of (b) (6) the Investigator confirmed that the event is still ongoing and that the final result is “benign” without any discussion or documentation of ultrasound findings or tissue diagnosis.
- 8) Goiter: Participant (b) (6) was a 41-year-old white male in the CT-P43 maintenance group, and his medical history included conjunctivitis, plaque psoriasis, anal fissure excision, nasal septal operation, nasal septum deviation, and obesity. His prior systemic immunosuppressant use included 4.7 months of cyclosporine, which was discontinued 57 days prior to starting CT-P43. On Day 265 (41 days after Week 16 dosing), he experienced a Grade 1 TEAE of “goiter.” The subject completed the trial. As

of (b) (6) the Investigator confirmed that the event is still ongoing, and no ultrasound findings, biopsy, or histopathology report is available.

Applying the Bradford-Hill criteria for causality to the TEAE imbalances

Steatohepatosis/Steatohepatitis/Fatty Liver Disease

1. Strength of association – The incidence rate for the TEAE is higher in the CT-P43 group, compared to the EU-Stelara group (no subject in the EU-Stelara group reported this TEAE), and the incidence rate for the EU-Stelara group falls outside of the 95th confidence interval of the incidence rate for the CT-P43 group, highlighting the notable risk difference.
 2. Consistency – There is only one clinical comparability trial conducted for the biosimilar, so this is not applicable.
 3. Temporality – All treatment-emergent adverse events meet this criterion with “effect” occurring after “cause.”
 4. Biological gradient – This TEAE occurred in one subject during Treatment Period 1 (TP1), and more subjects reported the TEAE during Treatment Period 2 (TP2). The accumulated drug effect leading to more incidence in the CT-P43 treatment group during TP2 is consistent with the biological gradient criterion.
 5. Plausibility & Analogy – Hypertriglyceridemia leading to adverse events such as steatohepatosis, acute pancreatitis, and gastroesophageal reflux symptoms have been well-documented (see the Reference in the BMER). CT-P43 caused higher incidence rates of hypertriglyceridemia and its associated GI and hepatic adverse events, compared to EU-Stelara. Case reports of Stelara’s association with hypertriglyceridemia and acute pancreatitis exist in literature; however, CT-P43, compared to EU-Stelara, seems to have a notably higher incidence in the clinical comparability trial.
 6. Coherence – The imbalances seen with hypertriglyceridemia and its associated GI and hepatic TEAEs, and treatment-emergent medications for liver, dyslipidemia, and GI symptoms, including proton pump inhibitors, provide coherence in that all these events were seen at higher rates in the CT-P43 treated group, compared to the EU-Stelara group.
 7. Experimental evidence – The Applicant submitted a 4-week repeat-dose toxicity study that was conducted in Cynomolgus monkeys with CT-P43 and EU-Stelara. Subcutaneous doses of vehicle, 45 mg/kg CT-P43, and 45 mg/kg EU-Stelara were administered to Cynomolgus monkeys (3/sex/group) once weekly for 4 weeks (4 doses in total). There were no reported CT-P43-specific findings from this study.
- However, the observed imbalances in the clinical comparability trial may not manifest in the non-clinical study, due to the following differences: a) the duration of the nonclinical study was only 28 days; b) there were only 6 monkey subjects per group and the size of the group may be too small for assessing the safety risk in question; c) the study was conducted in healthy monkeys that may not be as susceptible to worsening of metabolic syndrome observed in human subjects with psoriasis; and d) the species difference likely exists in how the effects of the humanized monoclonal antibody may manifest in the host subject.

Neoplasms (Malignant and Undefined, excluding benign tumors)

1. Strength of association – The incidence rate for the TEAEs is higher in the CT-P43 group, compared to the EU-Stelara group (no subject in the EU-Stelara group reported any (benign, malignant, or undefined) type of neoplasm), and the incidence rate for the EU-Stelara group falls outside of the 95th confidence interval of the incidence rate for the CT-P43 group, highlighting the notable risk difference.

2. Consistency – There is only one clinical comparability trial conducted for the biosimilar, so this is not applicable.
 3. Temporality – All treatment-emergent adverse events meet this criterion with “effect” occurring after “cause.”
 4. Biological gradient – This TEAE occurred in one subject (“cervical dysplasia” PT) during Treatment Period 1, and more subjects reported the TEAE during Treatment Period 2. The accumulated drug effect leading to more incidence in the CT-P43 treatment group is consistent with the biological gradient criterion.
 5. Plausibility & Analogy – Hypertriglyceridemia has been associated with development and progression of multiple malignant and benign tumors (see the references in the BMER). CT-P43 appears to cause higher incidence rates of hypertriglyceridemia and neoplasms, in addition to its associated GI and hepatic adverse events, compared to EU-Stelara.
 6. Coherence – The imbalances seen with neoplasms, hypertriglyceridemia and its associated GI and hepatic TEAEs provide coherence in that all these events were seen at higher rates in the CT-P43 treated group, compared to the EU-Stelara group.
 7. Experimental evidence – The Applicant submitted a 4-week repeat-dose toxicity study that was conducted in Cynomolgus monkeys with CT-P43 and EU-Stelara. Subcutaneous doses of vehicle, 45 mg/kg CT-P43, and 45 mg/kg EU-Stelara were administered to Cynomolgus monkeys (3/sex/group) once weekly for 4 weeks (4 doses in total). There were no reported CT-P43-specific findings from this study.
- However, the observed imbalances in the clinical comparability trial may not manifest in the non-clinical study, due to the following differences: a) the duration of the nonclinical study was only 28 days; b) there were only 6 monkey subjects per group and the size of the group may be too small for assessing the safety risk in question; c) the study was conducted in healthy monkeys that not be as susceptible to worsening of metabolic syndrome observed in human subjects with psoriasis; and d) the species difference likely exists in how the effects of the humanized monoclonal antibody may manifest in the host subject.

Clinical Reviewer’s Summary of TP2: The imbalances were seen with hyperlipidemia, hyperglycemia, hepatic steatosis, and Gastrointestinal Disorders SOC, suggesting overall worsening of metabolic syndrome in the CT-P43 group, compared to the EU-Stelara group. Also, the imbalance seen in the number of neoplasms is concerning, because the definitive tissue diagnosis is lacking for the majority of these neoplasms. Features of metabolic syndrome, including hypertriglyceridemia, have been associated with the initiation and progression of various malignancies and precancerous neoplasms, including prostate cancer, breast cancer, cervical cancer, colon cancer, etc. (Mwangi et al. 2024; Tran et al. 2023; Zhang et al. 2021; Zhang et al. 2022; Raju et al. 2014; Vanhemelrijck et al. 2011; Dong et al. 2021; Wuermli et al. 2005; Arthur et al. 2016; Salgado-Montilla et al. 2015; Hernandez-Perez et al. 2022; Guerrios-Rivera et al. 2023; Liu et al. 2023; Esposito et al. 2012; Russo et al. 2008; Agresti et al. 2016; Rosato et al. 2011; Lebdai et al. 2018; Tabuchi et al. 2008; Tabuchi et al. 2006; Hsu et al. 2022; Ahmet et al. 2006; Siddiqui et al. 2011; Kitayama et al. 2009; Wan et al. 2022; Zhan et al. 2024; Mazumder et al. 2023; Wu et al. 2022; Sun et al. 2020). It is notable that there were 2 cases of goiter in the CT-P43 group, compared to none in the EU-Stelara group. Hypertriglyceridemia and other features of metabolic syndrome have been associated with thyroid nodules in several studies (Tran et al. 2023; Zhang et al. 2021; Zhang et al. 2022); in one of these studies prevalence of thyroid nodules with ultrasound features suspicious for malignancy were as high as 36.9% (Tran et al. 2023).

During TP2 there was one subject (b) (6) in the CT-P43 group with an SAE of

hospitalization for respiratory failure (discussed under Serious Adverse Events). There was another subject (b) (6) in the CT-P43 group that developed TEAEs of GERD and chronic obstructive pulmonary disease (COPD) symptoms and were treated with esomeprazole, erdosteine, and tiotropium bromide. Of note, neither the subject with respiratory failure and asthma nor the subject with COPD had documented in their medical history prior respiratory conditions. It is well known that obesity or metabolic syndrome is associated with asthma or dyspnea, and this may be another indicator that metabolic syndrome was worsening in some of the subjects treated with CT-P43.

Table 43 Neoplasms Benign, Malignant, or Unspecified for CT-P43 3.1

Neoplasms benign, malignant or unspecified Dictionary-derived term	CT-P43		Stelara	
	TP1	TP2	TP1	TP2
Breast mass	0	1	0	0
Cervical dysplasia	1	0	0	0
Prostatic mass	0	1	0	0
Adrenal neoplasm	0	1	0	0
Colon adenoma	0	1	0	0
Neoplasm (Lung tumor)	0	1	0	0
Tubular breast carcinoma	0	1	0	0
Uterine leiomyoma	1	0	0	0
Goitre	0	2	0	0
TOTAL	2	8	0	0

Source: Clinical Reviewer

Comparison of CT-P43 maintenance and EU-Stelara maintenance over 52 weeks

In the Table 44, the AE imbalances between the CT-P43 maintenance and EU-Stelara maintenance group over the entire study period are shown. The switching group is not included, so that the AE incidence rate can be compared over 52 weeks. Similar imbalances in the areas of Gastrointestinal Disorders SOC, Hepatobiliary SOC, Metabolism and Nutrition Disorders SOC, Respiratory Disorders SOC, headache PT (the below number does not include migraine or “hypersensitivity” under headache PT), and injection site reactions PT.

Clinical Reviewer’s Comment: The overall pattern of imbalances observed during TP1 and during TP2 are mostly preserved when looking at the entire study period.

Table 44 TEAE Imbalances between CT-P43 Maintenance and EU-Stelara Maintenance (TP1 and TP2)

Summary of TEAEs - Group Terms

Group Term Preferred Term	CT-P43 - CT-P43 N = 253	Stelara- Stelara N = 125	Risk Difference	
	n (%)	n (%)	RD (95% CI)	Forest Plot
Gastrointestinal disorders	12 (4.7)	2 (1.6)	3.14 (-0.28, 6.56)	
Abdominal hernia	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	

Summary of TEAEs - Group Terms

Group Term Preferred Term	CT-P43 - CT-P43 N = 253	Stelara- Stelara N = 125	Risk Difference	
	n (%)	n (%)	RD (95% CI)	Forest Plot
Abdominal pain	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Abdominal pain upper	2 (0.8)	0 (0.0)	0.79 (-0.30, 1.88)	
Constipation	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Duodenitis	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Dyspepsia	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Food poisoning	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Gastric ulcer	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Gastritis	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Gastrointestinal disorder	0 (0.0)	1 (0.8)	-0.80 (-2.36, 0.76)	
Gastrooesophageal reflux disease	2 (0.8)	0 (0.0)	0.79 (-0.30, 1.88)	
Hiatus hernia	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Nausea	0 (0.0)	1 (0.8)	-0.80 (-2.36, 0.76)	
Pancreatitis acute	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Stomatitis	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Hepatobiliary Disorder	5 (2.0)	0 (0.0)	1.98 (0.26, 3.69)	
Hepatic cirrhosis	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Hepatic steatosis	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Hepatitis acute	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Non-alcoholic steatohepatitis	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	

Summary of TEAEs - Group Terms

Group Term Preferred Term	CT-P43 - CT-P43 N = 253	Stelara- Stelara N = 125	Risk Difference	
	n (%)	n (%)	RD (95% CI)	Forest Plot
Nonalcoholic fatty liver disease	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Hypertension	10 (4.0)	3 (2.4)	1.55 (-2.05, 5.15)	
Blood pressure increased	2 (0.8)	1 (0.8)	-0.01 (-1.91, 1.90)	
Hypertension	9 (3.6)	2 (1.6)	1.96 (-1.21, 5.13)	
General disorders and administration site conditions	4 (1.6)	0 (0.0)	1.58 (0.04, 3.12)	
Metabolism and nutrition disorders	16 (6.3)	4 (3.2)	3.12 (-1.18, 7.43)	
Hypercholesterolaemia	4 (1.6)	1 (0.8)	0.78 (-1.41, 2.97)	
Hyperglycaemia	2 (0.8)	0 (0.0)	0.79 (-0.30, 1.88)	
Hyperlipidaemia	2 (0.8)	0 (0.0)	0.79 (-0.30, 1.88)	
Hypertriglyceridaemia	7 (2.8)	1 (0.8)	1.97 (-0.59, 4.52)	
Hyperuricaemia	2 (0.8)	1 (0.8)	-0.01 (-1.91, 1.90)	
Insulin resistance	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Lipid metabolism disorder	1 (0.4)	1 (0.8)	-0.40 (-2.15, 1.34)	
Obesity	2 (0.8)	0 (0.0)	0.79 (-0.30, 1.88)	
Neoplasms (malignant or undefined)	4 (1.6)	0 (0.0)	1.58 (0.04, 3.12)	
Adrenal neoplasm	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Neoplasm	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Prostatic mass	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	

Summary of TEAEs - Group Terms

Group Term Preferred Term	CT-P43 - CT-P43 N = 253	Stelara- Stelara N = 125	Risk Difference	
	n (%)	n (%)	RD (95% CI)	Forest Plot
Tubular breast carcinoma	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Cervical dysplasia	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Nervous System Disorders	13 (5.1)	2 (1.6)	3.54 (0.04, 7.04)	
Anosmia	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Balance disorder	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Dizziness	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Guillain-barre syndrome	0 (0.0)	1 (0.8)	-0.80 (-2.36, 0.76)	
Headache	10 (4.0)	1 (0.8)	3.15 (0.29, 6.02)	
Migraine	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	
Vertigo	2 (0.8)	0 (0.0)	0.79 (-0.30, 1.88)	
Vertigo positional	1 (0.4)	0 (0.0)	0.40 (-0.38, 1.17)	

Source: Clinical Reviewer, OCS Analysis Studio, Safety Explorer.

Filters: ACTARM = "CT-P43 (Treatment1-CT-P43 (Treatment2" and SAFFL = "Y" (CT-P43 - CT-P43); ACTARM = "Stelara (Treatment1-Stelara (Treatment2" and SAFFL = "Y" (Stelara - Stelara); TRTEMFL = "Y" (Adverse Events).

Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Dropouts and/or Discontinuations

Healthy Volunteers (Studies CT-P43 1.1 and CT-P43 1.2): There were no discontinuations due to AEs in any of the studies conducted in healthy volunteers.

Subjects with PSO (Study CT-P43 3.1):

- Treatment Period 1: No subjects were reported to discontinue because of an adverse event. The EU-Stelara group had four (1.6%) dropout subjects: 3 subjects withdrew from the study, and 1 subject was lost to follow-up (Table 45). In the CT-P43 group, there were 3 (1.2%) dropout subjects: 2 subjects withdrew from the study, and 1 subject was terminated from the study by the investigator. The investigator cited "difficulty communicating" with the subject, who "is not cooperative with the study." This subject

(Participant (b) (6)) with a history of depression had a new onset of bipolar disorder.

- Treatment Period 2: The rate of treatment discontinuation due to AEs was slightly higher in the CT-P43 maintenance group (2.0%, 5 subjects), compared to the EU-Stelara maintenance (0.8%, 1 subject) or— Switched to CT-P43 (TP2) (0.8%, 1 subject) groups (Table 29). The AEs that led to the discontinuations are: Hepatitis B viral DNA positivity for the single subject in the EU-Stelara maintenance group; respiratory failure for the single subject in the Switched to CT-P43 ; prostate nodules, “hypersensitivity reaction” (Grade 3 headache, as discussed in Safety Analyses), Grade 3 headaches, positivity for Hepatitis B Surface Antigen, and Hepatitis B for the five subjects in the CT-P43 maintenance group. Of note, the subject with tubular adenocarcinoma in the CT-P43 (TP1) maintenance group was not included in this number, as she had received her final study dose on Day 295, 6 days prior to the SAE; otherwise, she would have discontinued the treatment due to this AE.

The rate of withdrawal from the study by subject was also slightly higher in the CT-P43 maintenance group (3.2%) than the EU-Stelara maintenanceTP2) (1.6%) or Switched to CT-P43 (0.8%) group.

Of note, severe TEAEs, SAEs, and death leading to study drug discontinuation were noted only in the CT-P43 treatment group, not in the EU-Stelara treatment group.

Table 45 Dropouts and Discontinuations for CT-P43 3.1

Reasons for Study Discontinuation	TP1		TP2		
	Stelara (n=253)	CT-P43 (n=256)	Stelara (Treatment1)-Stelara (Treatment2) (N = 125)	Stelara (Treatment1)-CT-P43 (Treatment2) (N = 124)	CT-P43 (Treatment1)-CT-P43 (Treatment2) (N = 253)
	n (%)	n (%)	n (%)	n (%)	n (%)
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Adverse event	0 (0%)	0 (0%)	1 (0.8%)	1 (0.8%)	6 (2.4%)
Physician decision	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0.0%)
Subject withdrawal	3 (1.2%)	2 (0.8%)	2 (1.6%)	1 (0.8%)	7 (2.8%)
Lost-to-follow-up	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	2 (0.8%)
Total	4 (1.6%)	3 (1.2%)	3 (2.4%)	2 (1.6%)	14 (5.5%)

Source: Clinical Reviewer

Clinical Reviewer's Comment: Overall, there were slightly higher rates for dropouts and discontinuations for the CT-P43 maintenance group, compared to the EU-Stelara maintenance or Switched to CT-P43 groups. TEAEs of Grade 3 or higher severity, SAEs, or death leading to discontinuation were noted only in the CT-P43 treatment group, and these included Grade 3 headaches for two subjects in the CT-P43 maintenance group.

6.3.3. Additional Safety Evaluations

Adverse Events of Special Interest (AESIs)

The prescribing information for US-Stelara carries the following warnings and precautions: infections (including cellulitis, pneumonia, sepsis, zoster, abscess, and tuberculosis), malignancies, hypersensitivity reactions, posterior reversible encephalopathy syndrome (PRES), and noninfectious pneumonia.

The Applicant identified the following AEs as Events of Interest: serious systemic hypersensitivity reactions, facial palsy, pustular or erythrodermic psoriasis, serious infection (including mycobacterial and salmonella infections), malignancy, cardiovascular events, reversible posterior leukoencephalopathy syndrome (RPLS), serious depression including suicidality, and venous thromboembolism.

Overall, the proportion of subjects experiencing AESIs were similar across all arms for the entire duration of the study (before and after re-randomization), with the exception of more COVID-19 infections in the EU-Stelara/ABP 654 arm in TP02 than the arms that continued on the same drug as in TP01.

Infections/serious infections

As shown in Table 22, all treatment groups in Study CT-P43 3.1 showed similar rates of Infection, overall. During TP1 of Study CT-P43 3.1, infections and infestations were reported at a rate of 14.5%; the CT-P43 treatment group had 15.2%, and the EU-Stelara group had 11.9%. COVID-19, followed by upper respiratory infection, was the most common dictionary-derived term cause. During TP2 of Study CT-P43, infections and infestations were reported at a rate of 18.7%; the CT-P43 treatment group had 18.3%, and EU-Stelara group had 20.8%. During TP2, COVID-19 (6.1%), upper respiratory infection (4.1%), and latent tuberculosis (2.9%) were the most common dictionary-derived term causes for Infections and infestations SOC.

Infections that were considered serious were rare during Study CT-P43 3.1, with comparable rates of serious infection across the treatment groups. COVID-19 pneumonia was the most common serious infection reported, at a rate of 0.8% in the study.

Clinical Reviewer's Comment: Overall, the data did not show clinically meaningful differences between the two products in terms of susceptibility to infections.

Injection site reactions

Overall, the AEs related to injection site reactions were more common with CT-P43 administration. In Study CT-P43 1.2 the rate of injection site reactions was 20% in the CT-P43 group, compared to 9% in the US-Stelara and 13% in the EU-Stelara groups (Table 31). In Study CT-P43 1.1 the rate of injection site reactions was slightly higher in the CT-P43 group (11.7 %), compared to the US-Stelara group (9.0%) and the EU-Stelara group (10.2%) (Table 30). The increased rates with CT-P43 repeated in Study CT-P43 3.1, albeit at low rates (Table 22). During TP1, the CT-P43 group had 1.2%, compared to 0.8% in the EU-Stelara group; during TP2, the CT-P43 group had 0.8%, compared to 0% in the EU-Stelara group.

Clinical Reviewer's Comment Given that the increased rates of injection site reaction for CT-P43, compared to EU-Stelara, were observed during the PK similarity studies and during both treatment periods for the clinical comparability study, there may be a small, but clinically meaningful difference between the two products.

Hypersensitivity reactions

Data submitted from the Applicant regarding this AESI focused on events that were thought to be related to study treatment. One event of drug "hypersensitivity" with the causality of "probable" in the CT-P43 treatment group resulted in treatment discontinuation during TP2 (Table 46).

When all Dictionary-Derived Term AEs that could be interpreted as symptoms of hypersensitivity irrespective of causality were assessed, these AEs were reported at similar rates across the treatment groups during TP1 and TP2 for Study CT-P43 3.1 (Table 46). Overall, AEs related to hypersensitivity were rare, and none of the events listed in Table 46 were considered to be an SAE.

Table 46 Hypersensitivity Reaction-Like Adverse Events for CT-P43 3.1

Dictionary-Derived Term AEs	TP1		TP2	
	EU-Stelara (n=253)	CT-P43 (n=256)	EU-Stelara (N = 125)	CT-P43 (N = 377)
	n (%)	n (%)	n (%)	n (%)
"Hypersensitivity"	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)
Urticaria	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)
Erythema	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)
Rash erythematous	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)
Pruritus	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)
Skin disorder	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)
Jessner's lymphocytic infiltration	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)
Dermatitis contact	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)
Allergy to Plants	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)
Swelling	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)
Asthma	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)
Sinusitis	0 (0%)	3 (1.2%)	1 (0.8%)	0 (0%)
Rhinitis	2 (0.8%)	3 (1.2%)	0 (0%)	2 (0.6%)
Rhinorrhea	1 (0.4%)	1 (0.4%)	0 (0%)	1 (0.3%)
Eosinophilia	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)
Total	6 (2.4%)	10 (4.0%)	3 (2.4%)	7 (2.1%)

Source: Clinical Reviewer

Malignancies

One TEAE related to malignancy, tubular breast carcinoma, was reported in the CT-P43 (TP1) – CT-P43 (TP2) treatment group during TP2. This is discussed in more detail above under **Serious Adverse Events**.

There were more undefined neoplasms that are suspicious for malignancies (breast mass, prostate mass, and cervical dysplasia) in the CT-P43 treatment group during TP2. These cases are discussed in more detail above under Neoplasms.

Clinical Reviewer's Comment: The imbalance seen in the number of malignant or undefined neoplasms is concerning, given the similar baseline characteristics of the subject populations for the CT-P43 and EU-Stelara groups, in terms of age, race, ethnicity, body weight, and prior use of immunosuppressants.

Table 47 Baseline Weight for Study CT-P43 3.1

Baseline Weight (kg)	Stelara (TP1) Stelara (TP2) N=125	Stelara (TP1) CT-P43 (TP2) N=124	CT-P43 (TP1) CT-P43 (TP2) N=253
Mean	86.2	85.0	85.4
Max	142.8	151.5	168
75th percentile	97.6	95.2	98.1
50th percentile (median)	86	85	85
25th percentile	72.7	70.6	70.3
Min	46.1	48	41

Source: Clinical Reviewer

Table 48 Prior Immunosuppressant Use for Study CT-P43 3.1

	Stelara (TP1) Stelara (TP2) N=125	Stelara (TP1) CT-P43 (TP2) N=124	CT-P43 (TP1) CT-P43 (TP2) N=253
Systemic Treatment for PS			
Treatment	N (%)	N (%)	N (%)
Biologic	21 (16.8)	23 (18.5)	38 (15.0)
Non-Biologic	72 (57.6)	72 (58.0)	152 (60.1)
Systemic Steroids	11 (8.8)	9 (7.3)	27 (10.7)
Duration of Systemic Treatment for PS			
Mean Duration (all systemic PS meds) in days	244	145	196
Median Duration (all systemic PS meds) in days	73	44	55

Source: Clinical Reviewer

Pregnancies

One spontaneous abortion was reported in the EU-Stelara group during TP1.

Clinical Reviewer's Conclusion on Safety during the Clinical Comparability Study: *The safety review found instances of improper coding, omissions, and insufficient follow-up of the TEAEs during the clinical comparability study, CT-P43 3.1. Lack of confidence in the quality and integrity of the safety data compromises the process of determining whether or not there is a clinically meaningful difference in terms of safety risk between CT-P43 and EU-Stelara. Furthermore, there were imbalances observed in multiple PT and SOC TEAE categories with higher numbers of incidence for the CT-P43 group, compared to the EU-Stelara group. There was a higher incidence rate of worsening hypertension in the CT-P43 group during TP1 that led to long-term antihypertensive medications. Some of these subjects experienced severe or persistent headaches or dizziness. Two subjects discontinued the study drug, due to persistent Grade 3 headaches. There were also higher incidences of hypertriglyceridemia and hyperglycemia in the CT-P43 group, and many of these subjects experienced Gastrointestinal Disorders SOC AEs and/or Hepatobiliary Disorders SOC AEs. Neoplasm SOC was another area of imbalance with one confirmed malignancy and three or more undefined neoplasms suspicious for possible malignancy, all occurring in the CT-P43 group. Although the deceased subject in the CT-P43 group had known risk factors for cardiovascular disease, the death from fatal myocardial infarction may be possibly related to CT-P43, given the worsening of features of metabolic syndrome observed in the CT-P43 group. Finally, severe TEAEs, SAEs, and death leading to study drug discontinuation were noted only in the CT-P43 treatment group, not in the EU-Stelara treatment group.*

In summary, in addition to the concerns regarding the data quality, there are safety risk imbalances observed during the clinical comparability study. CT-P43 demonstrated potentially significant increase in safety risk with worsening of features of metabolic syndrome and its associated conditions, compared to EU-Stelara (and thus US-licensed Stelara). Because worsening of metabolic syndrome, which is known to be prevalent in psoriasis patients, will be more difficult to attribute to its source of causation in a post-marketing setting, CT-P43 could effect negative health outcomes for patients for a long time without ever being withdrawn from marketing. Moreover, there are two other ustekinumab biosimilars that have already been approved, and CT-P43 will not add to the current treatment landscape of the diseases for which the Applicant is seeking indication. Therefore, this reviewer recommends, in the strongest term possible, against approval of CT-P43. CT-P43 has the potential to have a significant negative impact, without additional benefit, on public health.

Authors:
Sena Lee, MD, PhD
Clinical Reviewer

6.3.4. Cross Discipline Team Leader Assessment

The primary clinical reviewer has identified two areas of concern for her recommendation of a non-approvable action. This reviewer met with the primary clinical reviewer on several occasions to understand her position and assessment of the data and I have considered her assessment in detail. I do not believe that either issue rises to the level of rendering this application non-approvable. The first concern that the primary clinical reviewer has identified is that certain minor inconsistencies in the collection and reporting of data imply that there are significant data quality issues that

do not support approvability. Second, the primary clinical reviewer notes that certain imbalances in the PT and TEAE data in the comparative clinical study provide sufficient evidence to conclude that there are clinically meaningful differences between CT-P43 and US-licensed Stelara. The primary reviewer's conclusions about data integrity and CT-P43 are not supported by the data. While it is not feasible for this reviewer to address all instances in which I believe the clinical reviewer's methodology and/or conclusions were unsound, in my review below, I will address the main concerns identified by the primary clinical reviewer in Sections 6.3.1, 6.3.2, and 6.3.3.

On the first issue, in Section 6.3.1., the primary reviewer notes "There are multiple instances of omission, inappropriate coding, and insufficient follow-up of TEAEs, as noted above. Also, description of the nature, status, or outcome of the TEAEs varied depending on the source of data provided by the Applicant. There may be more cases not captured by this review. Thus, the safety analyses shown here may not provide a reliable depiction of safety risks associated with CT-P43."

This reviewer does not concur that the inconsistencies identified by the primary reviewer indicate a significant issue with data integrity. Clinical trials involve managing large volumes of data from multiple sources. This can be challenging due to human error, inconsistent data capture or subjects lost to follow-up. It is common to have minor but inconsequential inconsistencies or omissions in medical history collection, safety-event follow-up, or adverse event coding. The inconsistencies identified by the primary reviewer fall squarely in this category. Moreover, clinical inspections were conducted to assess the adequacy of data generated in the Study CT-P43 3.1. Thirty-four study centers in four countries (Estonia, Korea, Poland, and Ukraine) screened 574 subjects and enrolled 509 subjects. Of these study sites, the Office of Scientific Investigation (OSI) conducted site inspections at two select sites. The two clinical investigators selected for inspections (Drs. Jaworski and Daniluk) were selected based on size of enrollment at their study sites. OSI reviewed records of 85 subjects from both sites combined. The inspections did not find significant concerns regarding the oversight of the clinical study or GCP or regulatory compliance. There were no discrepancies in the submitted data when compared to the source data. No unusual enrollment practice or patterns were identified. OSI concluded that, based on the results of these inspections, data generated by the inspected clinical investigators were acceptable in support of the proposed application. Refer to the OSI inspection summary dated January 18, 2024.

The primary reviewer's expectation that scrutiny of all study sites is necessary for assurance in data quality is impractical and not in line with the Agency's standard practice. The most impactful sites in this study were sampled. This sampling along with a specified protocol and the applicant's internal monitoring measures is a reasonable approach to ensure data quality across study sites. Claiming that there is a data integrity issue due to not all sites being inspected, would be holding this applicant to a different standard. The number of records included in the inspection is a reasonable representation of the data and is sufficient to understand whether there were significant data integrity issues that would impact the Agency's assessment.

In Section 6.3.1, the primary clinical reviewer notes a single case of an inaccurate characterization of a subject discontinuation e.g., reported as “withdrawal by subject” instead of “due to adverse event”. This characterization does not impact the safety analysis. Total discontinuations were provided, occurred infrequently, and were similar across treatment arms. During Treatment Period I, a total of 7 subjects (1.4%) discontinued the study drug and terminated from the study prior to Week 16. The proportion of subjects with treatment or study discontinuation before Week 16 was similar between the CT-P43 group and EU-Stelara group. After re-randomization at Week 16, among the 502 subjects, 15 (3.0%) subjects discontinued the study drug (10 (4.0%), 3 (2.4%), and 2 (1.6%) in the CT-P43 maintenance, EU-Stelara maintenance, and switched to CT-P43 groups, respectively).

Therefore, the data and information in the application do not suggest any data quality issues that would preclude approval. Further, the single discontinuation case discussed above does not compromise the FDA’s ability to assess for whether clinically meaningful differences in safety exist between CT-P43 and US-Stelara. There is sufficient data and information in this application to conclude that the provided clinical data can be relied upon to support a demonstration that there are no clinically meaningful differences between CT-P43 and US-Stelara.

On the second issue, which the primary clinical reviewer seems to have considered as independent from the data quality issue discussed above, is a conclusion that there are clinical differences between CT-P43 and US-Stelara based on observed imbalances in the safety data from the comparative clinical study (CCS). Interpretation of comparisons beyond Week 16 are limited due to the crossover of EU-Stelara treated subjects to CT-P43 at Week 16 in Study CT-P43 3.1. This results in a higher number of patients who received 5 doses (up to Week 40) of study drug in the CT-P43 group as compared to the EU-Stelara group (243 patients and 121 patients, respectively). Furthermore, in this case, it is not appropriate to base such a conclusion of clinically meaningful differences solely on the CCS because the study lacks the sensitivity and is underpowered to demonstrate meaningful differences in individual adverse events. Rather, the totality of evidence submitted to support the application is proper and supports a demonstration that there are no clinically meaningful differences between CT-P43 and US-Stelara in terms of safety, purity, and potency. A summary of the evidence supporting this conclusion is described below:

- PK similarity between CT-P43 and US-Stelara was demonstrated in healthy subjects receiving a single 45 mg SC dose (Study CT-P43 1.2) and supports a demonstration of no clinically meaningful differences between CT-P43 and US-Stelara.

In repeat dosing of subjects with PsO (study CT-P43 3.1) serum trough concentrations in CT-P43 were comparable to the EU-Stelara group from Week 4 through Week 16 in treatment period 1 (TP1). While CT-P43 demonstrated a numerically higher trend in drug concentrations in TP1, the confidence intervals (CI) were overlapping. This numerically higher trend only holds true for TP1. Subjects on CT-P43 in treatment period 2 (TP2) have both higher and lower

levels than EU-Stelara at various timepoints. The serum concentrations were comparable in TP2 across the treatment groups of re-randomized subjects post Week 16 up to 40 weeks. Together, the results of the PK similarity study (Study CT-P43 1.2) and the CCS (Study CT-P43 3.1), help demonstrate no meaningful difference between CT-P43 and EU-Stelara.

- The comparative efficacy of CT-P43 and EU-Stelara was evaluated in Study CT-P43 3.1, a double-blind, randomized, multi-center, parallel-group, efficacy and safety study in subjects with moderate to severe plaque psoriasis (PsO) during 40 weeks of treatment. Comparative efficacy was assessed for the primary endpoint, the mean percent improvement in PASI at Week 12. The 90% confidence interval (CI) for the treatment difference based on the mean percent change from baseline in PASI at Week 12 for the Modified Intent-to-Treat (mITT) Analysis Set, the supportive per-protocol (PP) Analysis Set, as well as sensitivity analyses, all fall within the similarity margins of ± 10 [MITT: (-0.23, 4.32), PP: (-0.29, 4.29)]. Thus, the study demonstrated no meaningful differences between the CT-P43 and EU-Stelara as assessed by the primary efficacy endpoint. In addition, secondary efficacy endpoints, when considered with the primary endpoint results, also support a demonstration that there are no clinical meaningful differences between the CT-P43 and US-Stelara.
- Immunogenicity of CT-P43 was examined in PK similarity study (CT-P43 1.2, healthy male subjects) and the comparative clinical study (CT-P43 3.1, subjects with PsO). The development of binding and neutralizing ADAs was numerically lower or similar for the CT-P43 treatment groups compared with US-Stelara and EU-Stelara. The impact of study drug immunogenicity on PK, efficacy, and/or safety was generally comparable between CT-P43 and US-Stelara/EU-Stelara. Additionally, there were no meaningful differences in the rates of ADA in those subjects that underwent a single transition from EU-Stelara to CT-P43 in Study CT-P43 3.1., compared to those that remained on EU-Stelara. The numerical difference in ADA and Nab incidences in Studies CT-P43 3.1 and 1.2 are not considered to be clinically significant and does not preclude the conclusion of no clinical meaningful differences between CT-P43 and US-Stelara, as the systemic exposure between the treatment groups are comparable.

Moreover, additional data lend support to a conclusion that CT-P43 is biosimilar to US-Stelara:

- Celltrion performed a three-way analytical assessment comparing CT-P43, US-Stelara, and EU-Stelara using a comprehensive set of analytical methods. OPQ's assessment of the CT-P43 and US-Stelara data supports the determination that CT-P43 is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components. The minor differences identified are not expected to have a clinically meaningful impact.

- The CAA detected some the differences in glycans which is an expected result due to the proposed product being manufactured in a different cell line than the reference product. The impact of these differences for each glycan species was considered, and supporting data demonstrated that these differences do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge. In support of this conclusion there was no demonstration of Fc-mediated antibody effector functions; no differences in PK similarity, biological activity in-vitro, C1q binding biological activities and hypersensitivity (refer to the Quality Assessment for full details).
- There were also noted differences of C-terminal lysine and small differences in other post-translational modifications. These did not affect potency or PK and would not be expected to impact clinical safety.
- Lastly, there were only minor differences in purity. The levels of impurities in all products are low ((b) (4) %) and are not expected to have a clinically meaningful impact.
- The comprehensive battery of in vitro cell-free and cell-based studies are more sensitive in detecting product-related risks that may give rise to safety differences, should any exist because the CCS is underpowered to detect differences in individual adverse events.

Even looking at the CCS in isolation, the frequency of TEAEs, SAEs and discontinuations were generally comparable between the CT-P43 and EU-Stelara groups in the clinical study. Overall, serious adverse events were infrequent, and a single death occurred during the study. In Section 6.3.2, in reference to the single death, the primary clinical reviewer states “Although the subject had risk factors for myocardial infarction, such as obesity and smoking...[the] causality of death is that it’s possibly related to the study drug. This is based on the overall safety data imbalance with disproportionate worsening of cardiovascular risk factors, such as hypertension, hypertriglyceridemia, and hyperglycemia, observed in the CT-P43 treatment group”. The reviewer’s conclusion is inappropriate because there is insufficient evidence to causally link the death from myocardial infarction to CT-P43 or to worsening of risk factors brought on by CT-P43 treatment. Cardiovascular disease (CVD) is one of the major comorbidities in patients with psoriatic disease. In addition to having psoriasis, an independent risk factor for CVD, this subject also carried additional risk factors (obesity and tobacco use) confounding the attribution of causality. Another potentially confounding factor could be the contemporaneous administration of a vaccine which has been associated with cardiovascular adverse events for men of a similar age¹¹. This reviewer finds that the investigator’s conclusion that this death is unrelated to treatment

¹¹ Yasmin F. et al. Adverse events following COVID-19 mRNA vaccines: A systematic review of cardiovascular complication, thrombosis, and thrombocytopenia. *Immun Inflamm Dis*. 2023 Mar;11(3):e807.

with CT-P43 is reasonable. Furthermore, a single reported death is not sufficient to conclude that CT-P43 poses a different CVD risk than US-Stelara.

Adverse events that are likely to be associated with hyperpotency of a US-Stelara biosimilar such as various infections are either balanced or slightly higher in the EU-Stelara treatment arm. There are no safety differences related to immunogenicity or hypersensitivity. While some AEs, as pointed out by the primary reviewer (hypertriglyceridemia, headache, hypertension) trended higher in the CT-P43/ CT-P43 maintenance arms, others such as Covid-19 infections, oral herpes, CPK elevations trended higher in EU-Stelara/ EU-Stelara maintenance arms.

To understand whether CT-P43 AEs were associated with a higher exposure, Ctrough levels in the subjects with AESIs were analyzed. The observed Ctrough levels were variable and some subjects with lower Ctrough as compared to population mean also had AESIs. AEs in CCS could not be directly correlated to higher exposure. Therefore, the absence of dose-response-for-safety suggests that the observed AEs in the CT-P43 arm are more likely to be due to chance than to a novel safety profile.

In Section 6.3.2, , the primary reviewer noted imbalances in various AEs like hypertension and headache, Metabolism and Nutrition Disorders SOC, including hyperlipidemia, hypertriglyceridemia, and Gastrointestinal Disorders SOC (especially the ones involving upper GI inflammation) and Hepatobiliary Disorders SOC in TP1. Data comparisons from TP1 are easier to interpret due to the randomized study design. The primary reviewer implemented variable splitting and lumping of AEs to hypothesize that, based on reports of hypertriglyceridemia with symptoms of gastroesophageal reflux disease (GERD), hepatic steatosis, and pancreatitis, the imbalance in Metabolism and Nutrition Disorders SOC appears to be clinically meaningful. This reviewer does not agree with the primary reviewer's interpretation of the data and does not find the presented argument scientifically persuasive. Lumping of various AEs were not clinically appropriate and laboratory assessments do not support a signal associated with CT-P43. This reviewer concludes that the small numerical differences in various AEs in TP1 noted by the primary reviewer, between CT-P43 and EU-Stelara, are not clinically meaningful.

A single transition from EU-Stelara to CT-P43 was assessed as part of the study. Comparisons between CT-P43 and EU-Stelara in TP2 pose more of a challenge to interpret due to the cross-over design, the unequal exposure, and the loss of original randomization. This results in an imbalance in exposure between groups where most subjects are receiving CT-P43, meaning that there is a greater likelihood for events to occur on CT-P43 treatment as duration of exposure increases. The argument for an association with CT-P43 and metabolic effects/syndrome is not scientifically persuasive. The small numerical differences in select AEs in this portion of the study do not demonstrate a consistent pattern. No meaningful differences in the incidence of adverse events were observed in patients with PsO that underwent a single transition, compared to those that remained on their randomized treatment (CT-P43 or EU-Stelara).

For concerns raised by the primary reviewer, information requests were sent were sent to the applicant requesting additional details and analyses on various adverse events and laboratory values. The applicant's responses (received on 12/10/2023 and 12/14/2023) were reviewed and considered. The information provided in the responses showed that difference in TEAEs was small and an in-depth analyses into study drug relatedness did not identify a meaningful difference between the CT-P43 and EU-Stelara groups.

This reviewer does not agree with the primary reviewer's analysis of the data. For example, imbalances observed by comparing system organ class (SOC) groupings are not appropriate because SOC groupings contain AEs that are only related by the involved organ but are often unrelated by pathology and etiology; for example abdominal hernia and constipation are both under the SOC of gastrointestinal disorders but are not clinically related. Adverse events were inappropriately lumped in order to demonstrate an imbalance. This reviewer also finds limitations with the primary reviewer's assessment of causality in a number of AE cases. For many of the subjects whose TEAE is assessed by the primary reviewer as related to CT-P43, there are multiple confounders and there is a high possibility that the TEAE is related to a flare or progression of an already existing condition.

For example, the primary clinical reviewer notes in Section 6.3.2 that "the causality of the acute pancreatitis is that it is likely related to the study drug. This determination is based on the fact that this SAE occurred in the setting of higher than the measurable limits of serum triglyceride levels that were markedly increased from his Baseline ... The subject may have had chronic pancreatitis prior to the study, but the worsening of his condition leading to an SAE of acute pancreatitis is likely due to CT-P43, given the imbalance of hypertriglyceridemia observed in the CT-P43 treatment group." It is inappropriate to make conclusions about the potential causal relationship between the study drug and acute pancreatitis based on one subject, especially in the context of a patient with findings suggestive of a history of chronic pancreatitis. Chronic pancreatitis is characterized by a progressive fibro-inflammatory process and this acute flare is more likely to be related to a pre-existing condition.

The complexity of the cross-over study design should also be considered in the interpretation. This design is intended to provide a substantive descriptive assessment of whether a single transition would result in a major risk in terms of hypersensitivity, immunogenicity, or other reactions. It is not appropriate to attribute individual events to CT-P43 in subjects who have switched from treatment with EU-Stelara to CT-P43, or to consider individual events outside of the context of the switching arm as a whole. Furthermore, attribution of causality for expected long latency events, like malignancy, that occur after limited exposure are biologically implausible or unreasonable to associate the AEs with the study drug.

Lastly, there were also no clinically meaningful differences in laboratory parameters that correspond to the AEs that were of concern for the primary reviewer.

While no animal studies with CT-P43 and US-Stelara were needed to support this 351(k) application and the comprehensive battery of in vitro cell-free and cell-based studies are considered more sensitive than animal studies in detecting differences, the Applicant conducted a 4- toxicity study in monkeys using CT-P43 and EU-approved Stelara (EU-Stelara) and submitted the study report to the BLA. Study endpoints included mortality, clinical observations, body weight, food consumption, ophthalmic examination, body temperature, respiration rates, blood pressure, ECG, clinical pathology (hematology, coagulation, clinical chemistry, and urinalysis), and pathology examinations (organ weight, gross and histopathological examinations). The study results showed that the toxicity and toxicokinetic (TK) profiles of CT-P43 and EU-Stelara were similar.

In Section 6.3.3, the primary reviewer notes “Moreover, there are two other ustekinumab biosimilars that have already been approved, and CT-P43 will not add to the current treatment landscape of the diseases for which the Applicant is seeking indication.” Considering the approval status of other 351(k) BLAs is inappropriate when evaluating whether CT-P43 can be licensed as a proposed interchangeable biosimilar product. FDA evaluates whether the information submitted in the application is sufficient to demonstrate that the proposed biological product is biosimilar to and interchangeable with the reference product, without taking into account the availability of other approved biosimilars to the reference product.

In conclusion, the totality of the evidence demonstrates that CT-P43 is highly similar to US-licensed Stelara, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between CT-P43 and US-licensed Stelara in terms of the safety, purity, and potency of the product.

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CDTL

6.4. Clinical Conclusions on Immunogenicity

The immunogenicity evaluation included qualitative and quantitative measurement of anti-drug antibody (ADA) and neutralizing antibody (NAb) in healthy subjects (from single dose PK studies) and in subjects with plaque psoriasis (multiple doses up to 52 weeks), and an assessment of the impact of ADA on PK, efficacy and safety.

The safety analysis for Study CT-P43 3.1 included an evaluation of the frequencies of hypersensitivity, immune mediated reactions, and injection site reactions across treatment groups for all treatment periods. The incidence of hypersensitivity, immune-mediated reactions, and injection site reactions were infrequent. ADA positivity was not associated with increased reporting of hypersensitivity or injection site reactions.

It is concluded that the totality of immunogenicity data from the study, including following the single transition, support the conclusion that there are no clinically significant differences in the immunogenicity data between CT-P43 and EU-Stelara. Refer to Section 5.4 Immunogenicity Studies for results of the immunogenicity assessments.

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6.5. Risk in Terms of Safety or Diminished Efficacy of Switching Between Products and the Any Given Patient Evaluation (to Support a Demonstration of Interchangeability)

The Applicant has developed CT-P43 as a proposed interchangeable biosimilar to US-Stelara and is seeking licensure of CT-P43 for the same indications, same dosage form, strengths and routes of administration as US-Stelara.

The Applicant provided sufficient justification that CT-P43 can be expected to produce the same clinical result as US-licensed Stelara in any given patient. The scientific justification considered the factors that are described in the FDA guidance for industry, Considerations in Demonstrating Interchangeability with a Reference Product (refer also to Section 6.6 Extrapolation).

The Applicant also provided sufficient scientific justification that the risk in terms of safety or diminished efficacy of alternating or switching between use of CT-P43 and US-licensed Stelara is not greater than the risk of using US-licensed Stelara without such alteration or switch. The Applicant referenced the comparative analytical data provided in their application that evaluated and compared critical quality attributes of CT-P43 and US-Stelara and the results from the comparative clinical study (Study CT-P43 3.1) to support their justification. The Applicant also described that the results from the single transition included in Study CT-P43 3.1 provided supportive evidence of a low immunogenic risk and no safety concerns with switching between CT-P43 and US-Stelara.

FDA considers the risk of a clinically impactful immunogenic response when alternating or switching between CT-P43 and US-licensed Stelara to be low. Thus, a switching study that compares immunogenicity and PK and/or PD to assess the risk in terms of safety or diminished efficacy of alternating or switching between use of CT-P43 and US-licensed Stelara was considered unnecessary to support a demonstration of interchangeability for CT-P43.

The data and information provided by the Applicant are sufficient to demonstrate that CT-P43 can be expected to produce the same clinical result as US-Stelara in any given

patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of CT-P43 and US-Stelara is not greater than the risk of using US-Stelara without such alternation or switch.

6.6. Extrapolation

The Applicant submitted data and information in support of a demonstration that CT-P43 is highly similar to US-Stelara notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between CT-P43 and US-Stelara in terms of safety, purity and potency in patients with plaque psoriasis (Study CT-P43 3.1). In addition, the totality of evidence submitted in the application sufficiently demonstrates that CT-P43 can be expected to produce the same clinical results as US-licensed Stelara in any given patient and that, the risk in terms of safety or diminished efficacy of alternating or switching between use of CT-P43 and US-licensed Stelara is not greater than the risk of using US-licensed Stelara without such alteration or switch.

The Applicant is seeking licensure of CT-P43 for the following indication(s) for which US-Stelara has been previously licensed and for which CT-P43 has not been directly studied:

- Moderate to severe plaque psoriasis in pediatric patients 6 years and older, who are candidates for phototherapy or systemic therapy.
- Active psoriatic arthritis in adult patients and pediatric patients 6 years and older
- Moderately to severely active Crohn's disease in adults
- Moderately to severely active ulcerative colitis in adults

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of CT-P43 as an interchangeable biosimilar for each such indication for which licensure is sought and for which US-Stelara has been previously approved. This Applicant's justification was evaluated and considered adequate, and is summarized below.

Therefore, the totality of the evidence provided by the Applicant supports licensure of CT-P43 for each of the following indication(s) for which US-Stelara has been previously licensed and for which the Applicant is seeking licensure of CT-P43:

- Moderate to severe plaque psoriasis in adult patients and pediatric patients 6 years and older, who are candidates for phototherapy or systemic therapy.
- Active psoriatic arthritis in adult patients and pediatric patients 6 years and older
- Moderately to severely active Crohn's disease in adults
- Moderately to severely active ulcerative colitis in adults

6.6.1. DIVISION of RHEUMATOLOGY and TRANSPLANT MEDICINE (DRTM)

In addition to the plaque psoriasis indication, the Applicant is seeking licensure of CT-P43 (ustekinumab-stba) for the following indication under the purview of DRTM:

- Treatment of patients 6 years or older with active psoriatic arthritis (PsA)

In their application, the Applicant has provided justification for extrapolation of data and relevant supportive information for licensure of CT-P43 as an interchangeable biosimilar for the above indication for which licensure is sought and for which US-Stelara has been previously licensed and CT-P43 has not been directly studied.

First, as summarized above, the Applicant submitted data and information to demonstrate that CT-P43 is highly similar to US-Stelara and that there are no clinically meaningful differences between CT-P43 and US-Stelara in terms of safety, purity, and potency based on similar clinical pharmacokinetics (PK) (study CT-P43 1.2), and similar efficacy, safety, and immunogenicity in patients with moderate to severe plaque psoriasis (PsO) (study CT-P43 3.1).

Further, the additional points considered in the scientific justification for extrapolation of data and information to support licensure of CT-P43 for the treatment of PsA are described below.

Mechanism of Action (MOA)

CT-P43 is a recombinant humanized monoclonal immunoglobulin G (IgG) 1kappa antibody that binds to the p40 protein subunit used by both interleukin (IL)-12 and IL-23 cytokines. As these cytokines are involved in inflammatory responses, binding to p40 prevents downstream IL-12 and IL-23 activity and, thereby, attenuates an immune response.

In comprehensive *in vitro* comparative testing, CT-P43 has been shown to be functionally similar to ustekinumab. These data demonstrate that the biologic activity and potency of CT-P43 have a high degree of similarity to ustekinumab and provide additional evidence that the MOA of the two products, binding to the p40 subunit of the IL-23 and IL-12 and, subsequently, preventing the interaction of IL-23 and IL-12 with IL-12Rb1, is the same.

The Applicant adequately addressed each of the known and potential mechanisms of action of Stelara and submitted data to support the conclusion that CT-P43 and US-Stelara have the same mechanisms for the sought indication of PsA to the extent that the mechanisms of action are known or can reasonably be determined.

Pharmacokinetics (PK)

The clinical development program to support similarity of CT-P43 to US-Stelara includes

a PK study in healthy male subjects and one comparative clinical study in subjects with moderate to severe PsO. Similar PK was demonstrated between CT-P43, EU-Stelara, and US-Stelara in study CT-P43 1.2, a randomized, double-blind, parallel group, 3-arm PK similarity study in healthy Japanese males. This study is reviewed in the section on Clinical Pharmacology. Importantly, CT-P43 was demonstrated to be highly similar to US-Stelara, as discussed in the section on CMC/Product Quality; therefore, there are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between CT-P43 and US-Stelara in the rheumatology indication for licensure (PsA). Thus, a similar PK profile would be expected between CT-P43 and US-Stelara in patients with PsA.

The Applicant provided adequate justification that a similar PK profile is expected between CT-P43 and US-Stelara for PsA.

Immunogenicity

Immunogenicity of CT-P43 was examined in the PK similarity study CT-P43 1.2, healthy male subjects) and comparative clinical study (CT-P43 3.1, subjects with PsO), and development of binding and neutralizing ADAs was numerically lower or similar for the CT-P43 treatment groups compared with US-Stelara and EU-Stelara. As reviewed elsewhere in this document, the clinical PK and safety data support that the observed differences are not clinically meaningful. The Agency has concluded that there are sufficient data to support similar immunogenicity between CT-P43 and US-Stelara with repeat dosing in subjects with PsO and after a single dose in healthy subjects. Accordingly, similar immunogenicity would be expected between CT-P43 and US-Stelara in patients with PsA. In addition, DRTM notes that similar rates of antibodies to US-Stelara were seen in clinical studies of subjects with PsO and PsA.[\[1\]](#)

The Applicant provided adequate justification that similar or decreased immunogenicity is expected between CT-P43 and US-Stelara for PsA.

Toxicity

The Applicant demonstrated that there are no meaningful differences in safety between CT-P43 and EU-Stelara in subjects with PsO and between CT-P43, EU-Stelara, and US-Stelara following single doses in healthy subjects. Additionally, in controlled clinical studies of US-Stelara submitted to support its approval, as described in the approved labeling,¹² the types of adverse events and their rates were similar across indications. Coupled with the demonstration of analytical and PK similarity between CT-P43, US-Stelara, and EU-Stelara, a similar safety profile would be expected between CT-P43 and US-Stelara in patients with PsA.

The Applicant provided adequate justification that a similar safety profile would be expected between CT-P43 and US-Stelara for PsA.

¹² FDA-approved US-Stelara labeling

Additional factors considered (if applicable)

None

Conclusions

Based on the above considerations, DRTM concludes that the Applicant has provided sufficient scientific justification (based on the mechanism of action, pharmacokinetics, immunogenicity, and toxicity profile) for extrapolation of the data and information to support licensure of CT-P43 for the rheumatologic indication of psoriatic arthritis for which US-Stelara has been previously licensed and for which the Applicant is seeking licensure.

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Suzette Peng, MD
Clinical Team Leader, DRTM

Raj Nair, MD
Acting Deputy Division Director, DRTM

6.6.2. Division of Gastroenterology

Executive Summary: Consistent with the principles of the FDA guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015),¹³ the Division of Gastroenterology (DG) concludes that the Applicant has provided sufficient scientific justification to support extrapolation of data submitted in the application to support licensure of CT-P43 as an interchangeable biosimilar to US licensed Stelara, under section 351(k) of the PHS Act, for the non-studied indications of Crohn's disease (CD), and ulcerative colitis (UC) in adults. The scientific justification based on the mechanism of action, pharmacokinetics (PK), immunogenicity, and safety supporting this conclusion are summarized in the following paragraphs.

Mechanism of Action: The mechanisms of action of ustekinumab that are relevant to moderate to severe active plaque psoriasis (PsO; the studied clinical study population) are also relevant to inflammatory bowel disease (IBD) (i.e., CD and UC). The Applicant provided data to support that CT-P43 has the same known and potential mechanisms of action as US-Stelara, which supports extrapolation to indications not directly studied in the CT-P43 clinical program. Ustekinumab belongs to the pharmacologic class of interleukin (IL)-23 and IL-12 antagonists. It is a human IgG1 κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4⁺ T-cell differentiation and activation. In the *in vitro* models, ustekinumab was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine

¹³ Guidance for Industry – Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.

cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-12R β 1. The cytokines IL-12 and IL-23 have been implicated as important contributors to the chronic inflammation that is a hallmark of CD and UC.¹⁴ The biological activities of CT-P43 and US-Stelara were evaluated by a comprehensive set of comparative functional and binding assays. The product quality reviewers concluded the acceptability of the comparative analytical assessments. Biological activities relevant to the primary mode of action i.e., IL-12 and IL-23 receptor binding and inhibition assays, as well as those related to IFN- γ secretion inhibition and IL-12/IL-23 inhibition reporter assays were similar across CT-P43 vs. US-Stelara. Overall, these data support the determination that CT-P43 and US-Stelara are highly similar. Data support the conclusion that CT-P43 and US-Stelara utilize the same mechanism(s) of action, to the extent such mechanism(s) are known.

Pharmacokinetics (PK): Study CT-P43 1.2., was a randomized, double-blind, parallel group, single dose, PK similarity study conducted in healthy Japanese adult male subjects. The clinical pharmacology reviewers concluded that the data from this study support a demonstration of PK similarity between CT-P43 vs. US-Stelara, CT-P43 vs. EU-Stelara, and US-Stelara vs. EU-Stelara in healthy subjects (refer to Section 5 Clinical Pharmacology Evaluation and Recommendations). Available data on US-Stelara do not indicate any major differences in PK based on disease state. It is reasonable to conclude that PK for CT-P43 is expected to be similar between patients with PsO (the studied population) and those with IBD.

Immunogenicity: In the CT-P43 development program, immunogenicity was evaluated in populations that were considered sensitive for detecting meaningful differences (healthy subjects and PsO). While some differences were noted in the ADA incidence across the treatment groups in both study populations, per the Clinical Pharmacology reviewers, the impact of immunogenicity on PK, efficacy, and/or safety between CT-P43 and US-/EU-Stelara was generally comparable and not considered to be clinically meaningful. Additionally, there were no meaningful differences in the rates of ADA in those subjects that underwent a single transition from EU-Stelara to CT-P43 in Study CT-P43 3.1., compared to those that remained on EU-Stelara. Therefore, it is reasonable to conclude that the impact of immunogenicity in patients with IBD receiving CT-P43 would be similar to that observed in patients with PsO receiving US-Stelara. Refer to Section 5 Clinical Pharmacology Evaluation and Recommendations of this review for further details.

Safety: The safety of CT-P43 compared to EU-Stelara was assessed in the comparative clinical study CT-P43 3.1. conducted in patients with PsO, and supported by a single dose, PK similarity study CT-P43 1.2. conducted in healthy subjects. Safety assessments in the two clinical studies included adverse events (AEs), physical examinations, vital signs, clinical laboratory testing, and immunogenicity assessments. The frequency of TEAEs, SAEs and discontinuations due to AEs were generally comparable between the CT-P43 and EU-Stelara groups in the clinical study. In

¹⁴ Stelara USPI approved 03/06/2023, available on Drugs@FDA.

addition, as previously noted, a single transition from EU-Stelara to CT-P43 was assessed as part of the study. No meaningful differences in the incidence of adverse events, were observed in patients with PsO that underwent a single transition, compared to those that remained on their randomized treatment (CT-P43 or EU-Stelara). Refer to the Section 6.3. Review of Safety Data, for further details. In controlled clinical studies of US-licensed Stelara, as described in the approved labeling, the types of adverse events and their rates were similar across indications. The safety profile of CT-P43 has been shown to be similar to that of EU-Stelara in patients with PsO. When combined with the adequate PK bridging between US-Stelara and EU-Stelara from the healthy subject study CT-P43 1.2., as well as similar product quality attributes, PK, and immunogenicity, the safety profile in the IBD population is expected to be generally comparable to that observed in patients with PsO, and overall, the data support extrapolation to the non-studied IBD population.

Regulatory Recommendations: DG concludes that sufficient scientific justification was provided to support licensure of CT-P43 for the following indications:

- For the treatment of adult patients with moderately to severely active Crohn's disease.
- For the treatment of adult patients with moderately to severely active ulcerative colitis.

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7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, ustekinumab-stba, was conditionally accepted by the Agency (DMEPA review dated April 4, 2024).

7.2. Proprietary Name

The proposed proprietary name for CT-P43 is conditionally approved as STEQEYMA. The name has been reviewed by DMEPA, who concluded the name was acceptable (DMEPA review dated September 27, 2023).

7.3. Other Labeling Recommendations

In light of the recommendation for a Complete Response, the labeling review was deferred until the next review cycle.

Author:

Amy Weitach, DO, MS
Clinical Team Leader

8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 13.2 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

Author:

Amy Weitach, DO, MS
Clinical Team Leader

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was held for this biosimilar application, as it was determined that there were no issues where the Agency needed input from the Committee.

Author:

Amy Weitach, DO, MS
CDTL

10. Pediatrics

This application included the “Amended Initial Pediatric Study Plan (iPSP) Version 5.0,” agreed to on March 28, 2022. The Agency agreed to the deferral for the 45mg/0.5ml vial presentation.

In this application, the Applicant included assessment via extrapolation for pediatric patients ages 6-17 years with plaque psoriasis and psoriatic arthritis. See Section 6.6 for review of the assessments.

Subsequent to submission of the BLA, on February 16, 2024, the Applicant submitted an amendment to the Amended iPSP requesting to retract the deferral plan for the 45mg vial presentation in an amended iPSP because the Applicant has completed studies on the 45mg vial presentation. However, this data has not been submitted to the Agency for review.

The Applicant noted that the labeling for US-Stelara does not include adequate pediatric information and is not licensed for the treatment of:

- Plaque psoriasis in pediatric patients < 6 years of age
- Psoriatic arthritis in pediatric patients < 6 years of age
- Crohn’s disease in pediatric patients 0-17 years of age
- Ulcerative colitis in pediatric patients 0-17 years of age

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a “new active ingredient” for purposes of PREA, and a pediatric assessment is generally required. However, since this application will receive a complete response, issuance of a PMR is not applicable.

Author:

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CDTL

11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None.

11.2. Recommendations for Postmarket Requirements and Commitments

Not Applicable due to CR action.

Author:

Amy Weitach, DO, MS
Clinical Team Leader

12. Comments to Applicant

In the action letter the Division has provided our reasons for the action and, where possible, our recommendations to address these issues. The following comments will be conveyed:

PRODUCT QUALITY MICROBIOLOGY

- (1) The bacterial retention study is inadequate for the CT-P43 IV drug product (5 mg/mL).

(b) (4)

(b) (4)

Repeat the bacterial retention study of the

(b) (4)

for CT-P43 IV drug product vial (5 mg/mL).

- (2) The container closure integrity test (CCIT) dye ingress method used for stability testing of CT-P43 IV drug product vials is not validated to ensure reproducibility of results between different analysts. The validation summary for the dye ingress method in Table 3.2.P.5.3-59 includes results for sensitivity, specificity, and robustness, however the reproducibility of the visual detection method between different analysts is not addressed. According to FDA Guidance for Industry Analytical Procedures and Methods Validation for Drugs and Biologics (2015), for non-compendial method, validation data are needed to support the reproducibility of the method. Provide evidence of the reproducibility of the visual inspection method to detect breach sizes at the limit of detection with multiple analysts. Alternatively, measure all samples by spectrophotometry and provide an updated

method description with acceptance criteria and submit additional method validation data accordingly.

PRODUCT QUALITY

- (3) The proposed release and stability specification for clarity of (b) (4) for CT-P43 drug product (DP) [SCS] is not acceptable because it is not justified by your clinical and manufacturing experience. In your response to information request (IR), received on 05/13/2024, you proposed not to tighten this release and stability specification based on stability data under stress condition ($40\pm 2^\circ\text{C}/75\pm 5\%\text{RH}$) for Lot No. 2NGP01 as justification. The proposed justification is not acceptable as it is not clinically relevant. Results from accelerated and stress conditions should not be used to support the release and long-term stability acceptance criteria. In addition, this specification is not supported by the updated full term (36 months) stability data from the primary stability (non-PPQ) batches provided in the same amendment in SN 0027, which consistently showed results are below (b) (4) NTU at all timepoints throughout the product shelf life. Tighten the release and stability acceptance criteria for clarity for CT-P43 [SCS] DP based on the historical release and long-term stability results to ensure consistent quality of CT-P43 DP [SCS].
- (4) The proposed shelf-life limit of (b) (4) % for acidic peaks in CT-P43 PFS and Vial DP is not supported by your clinical and manufacturing experience. In the IR response received on 05/13/2024, you proposed not to tighten this shelf-life limit based on results from the stress and accelerated conditions. You described that the (b) (4) are associated with an (b) (4). However, the proposed shelf-life limit does not reflect the clinical and manufacturing experience and is not supported by the updated full term stability results (all data points $\leq$ (b) (4) %) from the primary stability batches (non-PPQ) for both PFS and vial DP presentations provided in the same amendment in SN 0027. Tighten the shelf-life acceptance criteria for acidic peaks based on long term stability data to ensure the consistent CT-P43 DP quality over the shelf-life.

13. Signatory Comments

The applicant is seeking a licensure of CT-P43 as a biosimilar to and interchangeable with US-licensed Stelara as follows:

- CT-P43, 45 mg/0.5 mL PFS for subcutaneous use as interchangeable with US-Stelara 45 mg/0.5 mL PFS for subcutaneous use,

- CT-P43, 90 mg/mL PFS for subcutaneous use as interchangeable with US-Stelara 90 mg/mL PFS for subcutaneous use, and
- CT-P43, 130 mg/26 mL single-dose vial for intravenous (IV) use as interchangeable with US-Stelara 130 mg/26 mL single-dose vial for IV use, and for the indications approved for Stelara:
 - moderate to severe plaque psoriasis (Ps) in adult patients and pediatric patients 6 years and older, who are candidates for phototherapy or systemic therapy,
 - active psoriatic arthritis (PsA) in adult patients and pediatric patients 6 years and older,
 - moderately to severely active Crohn's disease (CD) in adults, and
 - moderately to severely active ulcerative colitis in adults.

I concur with the recommendation by the Office of Pharmaceutical Quality (OPQ) that the data submitted in this application are not sufficient to support the conclusion that the manufacture of CT-P43 is well-controlled and leads to a product that is pure, safe, and potent. OPQ review of submitted data identified multiple product quality deficiencies including inadequate qualification of reference standards, inadequate control of drug product, and insufficient data to support sterility assurance of the CT-P43 130 mg/26 mL single-dose vial drug product. OPQ is not recommending an approval of this BLA until the product quality deficiencies are satisfactorily resolved.

Therefore, this BLA application will be issued a complete response (CR) based on identified product quality deficiencies. Specific deficiencies and what would be required to resolve them will be listed in CR letter.

I concur with the CDTL's recommendation that the submitted clinical data is sufficient to conclude that the investigational product CT-P43 can be approved as an interchangeable biosimilar product.

I do not concur with the primary clinical reviewer's opinion that there are clinically meaningful differences between CT-P43 and the reference product due to safety concerns.

The CDTL portion of this review elaborates in detail on the key issues raised by the primary clinical reviewer and I agree with the CDTL's assessment. To discuss the analysis and interpretation of the data submitted, the review team had several internal meetings with the clinical reviewer. After open discussion about the data, the team was unable to reach alignment with the clinical reviewer. I have carefully considered her analysis and views along with the analysis and views of other members of the review team in reaching the conclusion that the clinical data are sufficient to support approval of CT-P43 as an interchangeable biosimilar product.

The potential issue with data integrity raised by the primary reviewer is not supported by the OSI Division after they conducted an inspection of 2 sites with the largest study enrollment.

The primary reviewer's concern about an imbalance in certain adverse events does not suggest that there are clinically meaningful differences between CT-P43 and US-Stelara. As the CDTL review explains, the study conducted by the applicant is not sufficiently powered for safety and the imbalance in adverse events such as headaches, elevated blood pressures, etc. does not raise safety concerns that would preclude approval. These adverse events that are identified by the primary reviewer, by regulatory definition of severity, are not severe, do not appear in clusters, and do not

suggest that there is a clinically meaningful difference between CT-P43 and US-Stelara. Imbalances such as those indicated in the clinical review are common and could, in part, be explained by the greater number of subjects who received CT-P43 vs EU-Stelara in the comparative clinical study.

In conclusion, the data and information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrate that CT-P43 can be approved as an interchangeable biosimilar product, once the deficiencies described in the Complete Response letter are addressed.

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14. Appendices

14.1. References

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14.2. Financial Disclosure

Covered Clinical Study : CT-P43 1.1

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>23</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: CT-P43 1.2

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 54		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____

Significant payments of other sorts: _____

Proprietary interest in the product tested held by investigator: _____

Significant equity interest held by investigator in S

Sponsor of covered study: _____

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: CT-P43 3.1

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>161</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____		

Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Author:
Sena Lee, MD, PhD
Clinical Reviewer

14.3. Nonclinical Appendices

14.3.1. Nonclinical Pharmacology

In Vivo Pharmacology

No data provided.

14.3.2. Nonclinical Pharmacokinetics

No data provided.

14.3.3. General Toxicology

Single-Dose Toxicity/Toxicokinetics

No data provided.

Repeat-Dose Toxicity/Toxicokinetics

A 4-week repeat-dose toxicity study was conducted in Cynomolgus monkeys with CT-P43 and EU-Stelara (Study# 8416958, GLP). Subcutaneous doses of 0 (vehicle: 4.36 mM L-histidine HCL monohydrate, 2.35 mM L-histidine, 7.6% sucrose, and 0.004% polysorbate 80 in sterile water for injection, pH 5.7 ± 0.3), 45 mg/kg CT-P43 and 45 mg/kg EU-Stelara were administered to Cynomolgus monkeys (3/sex/group) once weekly for 4 weeks (4 doses in total).

Study endpoints included mortality, clinical observations, body weight, food

consumption, ophthalmic examination, body temperature, respiration rates, blood pressure, ECG, clinical pathology (hematology, coagulation, clinical chemistry, and urinalysis), and pathology examinations (organ weight, gross and histopathological examinations). TK parameters were also evaluated.

There were no significant treatment-related findings. The toxicity profiles of the two products were similar. The TK parameters were evaluated for Days 1 and 22 (see the table below). The TK profiles of the two products at the 45 mg/kg dose were similar as well. Drug accumulation was noted after repeated dosing. The test article comparison ratio (CT-P43/EU-Stelara) values ranged from 0.94 to 1.02 for C_{max} and 0.97 to 1.00 for $AUC_{0-168hr}$ (sex-combined).

TK parameters of CT-P43 and EU-Stelara in Cynomolgus monkeys:

Day	Dose Group	Dose Level (mg/kg/dose)	Sex	C_{max} ($\mu\text{g/mL}$)	T_{max} (h)	AUC_{0-168} ($\text{h} \cdot \mu\text{g/mL}$)
1	2	45 (Stelara®)	M	506	88.0	71600
			F	534	56.0	68900
			MF	520	72.0	70200
	3	45 (CT-P43)	M	449	88.0	63400
			F	531	40.0	73400
			MF	490	64.0	68400
22	2	45 (Stelara®)	M	1290	72.0	187000
			F	1240	40.0	172000
			MF	1270	56.0	180000
	3	45 (CT-P43)	M	1130	32.0	151000
			F	1460	56.0	208000
			MF	1300	44.0	180000

14.4. Clinical Pharmacology Appendices

Author: Sanjida Mahjabeen, PhD (Primary Reviewer) /Chinmay Shukla, PhD (Clinical Pharmacology Team lead)

14.4.1. Other PK similarity Study: Study CT-P43 1.1

Study CT-P43 1.1 (Part 2)

The study CT-P43 1.1 was a 3-arm, parallel design PK study conducted in New Zealand in healthy male subjects. This study was conducted in two parts. In part 1, safety, tolerability, and PK of CT-P43 was assessed following single dose upto 4 weeks. The aim of Part 2 was to assess the PK similarity among CT-P43, US-Stelara and EU-Stelara. In Part 2, blood samples for PK and ADA assessments of CT-P43, EU-approved Stelara, and US-licensed Stelara were collected from all subjects at Day 1 Pre-dose and post dose (within 60 minutes prior to administration of the study drug and

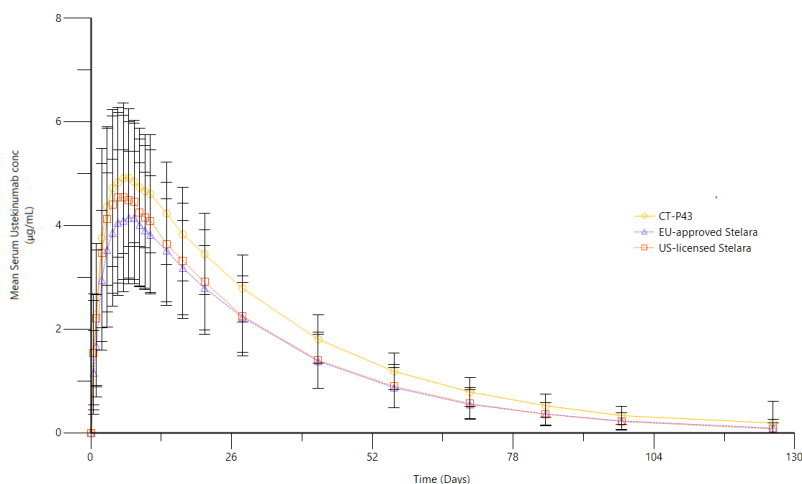
12 hours after the administration of the study drug); on Day 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 18 and 22, 29, 43, 57, 71, 85, and 127 or end of study time. The point estimates and 90% CIs of the GMRs of AUC_{inf} , and AUC_{0-t} were not contained within the pre-defined criteria of 0.8 to 1.25 (Table 35), thus PK similarity was not demonstrated among CT-P43, US Stelara and EU Stelara. The mean serum concentration-time profiles shows that CT-P43 treated subjects had higher exposure compared to the EU-Stelara and US licensed Stelara treated subjects.

Table 49: Summary of statistical analyses for assessment of PK similarity (Study CT-P43 1.1)

	Geometric Least Square Mean (Geometric CV%)			Geometric Least Square Mean Ratio* T/R ratio (90% CI upper - 90% CI lower)		
Primary						
	CTP43 (N=80)	US Stelara (N=77)	EU Stelara (N=81)	CTP43 vs US Stelara	CTP43 vs EU Stelara	US Stelara vs EU Stelara
AUC _{0-inf} (µg.day/mL)	198.30	155.29	151.86	127.69 (117.04-139.3)	130.57 (120.29-141.73)	102.25 (93.78-111.49)
Cmax (µg/mL)	5.14	4.47	4.24	114.85 (105.28-125.29)	121.34 (111.79-131.71)	105.64 (96.92-115.15)
Secondary						
AUC _{0-127days} (µg.day/mL)	189.50	141.81	140.62	133.62 (117.85-151.50)	134.74 (119.71-151.69)	100.84 (89.05-114.21)

Source: FDA Analysis using ADPC.xpt from Study CT-P43 1.1

Figure 12: Mean (+/- SD) Serum Concentration of Ustekinumab ($\mu\text{g}/\text{mL}$) in Study CT-P43 1.1



Source: FDA Analysis using ADPC.xpt from Study CT-P43 1.1

Table 50: Statistical Summary of PK Parameters of Study Drug by Treatment Arm in Study CT-P43 1.1

PK Parameters	CT-P43 (N=94)	EU-approved Stelara (N=98)	US-licensed Stelara (N=77)
	Geometric Mean (Geometric CV%)		
AUC_{inf} (µg.day/mL)	198.3 (27.26)	151.87 (36.96)	155.3 (41.81)
AUC_{0-127days}	189.5 (28.49)	140.63 (57.98)	141.82 (69.74)
CL/F (mL/day)	226.93 (27.26)	296.31 (36.96)	289.77 (41.81)
C_{max} (µg/mL)	5.14 (28.43)	4.24 (35.56)	4.48 (42.58)
t_{1/2} (Day)	22.43 (21.34)	20.24 (23.87)	19.45 (27.38)
λ_z	0.03 (21.34)	0.03 (23.87)	0.04 (27.38)
T_{max} (Day)	7.69 (37.1)	7.96 (33.84)	7.32 (39.83)
V_z/F (mL)	7341.87 (24.84)	8651.99 (28.7)	8130.47 (32.29)

Source: FDA Analysis using ADPC.xpt Study CT-P43 1.1

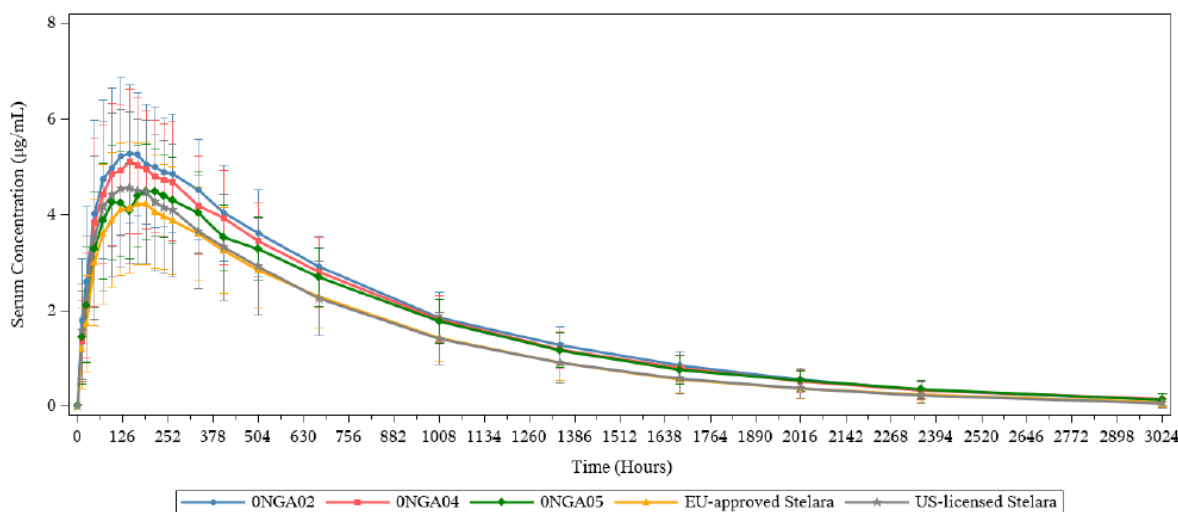
Following study CT-P43 1.1, the applicant investigated the root cause for failure in PK similarity demonstration. It was determined that generally, there was greater protein content in the clinical batches of CT-P43 which were used in the Study CT-P43 1.1 compared to the protein content values of EU-Stelara and US-Stelara batches. Following Table 37 shows a comparison among the three products with regards to protein content. It shows that CT-P43 batch 0NGA05 had closer value of protein content when compared with the US-Stelara and EU stelara while the other CT-P43 batches had notably larger protein content values than those of EU-Stelara and US-Stelara batches.

Table 51. Protein content of clinical batches used in Study CT-P43 1.1 (Part 2)

	CT-P43 (0NGA02 ^{1,2})	CT-P43 (0NGA04 ²)	CT-P43 (0NGA05 ²)	EU-Stelara (JFS1VVK ^{1,2})	US-Stelara (JCS0UME ²)
Extractable volume (mL/syringe) (A)	0.54 ³	0.54 ³	0.53 ³	0.52 ⁴	0.51 ⁴
Protein Concentration (mg/mL) (B)	93 ⁵	92 ⁵	89 ⁵	91 ⁶	91 ⁶
Protein Content (mg/syringe) (A x B)	50.22	49.68	47.17	47.32	46.41
Ratio of Protein Content Compared to EU-Stelara	106.13%	104.99%	99.68%	100%	98.08%
Ratio of Protein Content Compared to US-Stelara	108.21%	107.05%	101.64%	101.96%	100.00%
Number of Subjects Who Received the Study Drug (PK Set)	23	37	20	81	77

Source: BLA761338 eCTD Section 5.3.5.4 Investigation Report on Pharmacokinetic Results from Study CT-P43 1.1 Part 2.

When the serum concentration of study drug and PK parameters were analyzed by batch, it was found that subjects who were treated with CT-P43 batch 0NGA05, the difference between CT-P43, US-Stelara and EU-Stelara was smaller with regards to AUC and C_{max}. This suggests that the higher protein content in the CT-P43 clinical batches likely contributed to the differences in PK observed between CT-P43 and US-Stelara and EU-Stelara in Study CT-P43 1.1. In the subsequent PK similarity study CT-P43 1.2, US-Stelara, EU-Stelara, and CT-P43 batches with similar protein content were used; no formulation change to CT-P43 was made.

Figure 13. Mean (+/- SD) Serum Concentration of study drug (µg/mL) by Batch in Study CT-P43 1.1

Source: CT-P43 Post-hoc analysis - Study 1.1¹⁵;

Immunogenicity assessment in Study CT-P43 1.1

Samples for immunogenicity assessment were collected predose on Day 1 (pre-dose), Day 15, Day 29, Day 57, Day 85, Day 127

Incidence of ADA and Nab in Study CT-P43 1.1

In Study CT-P43 1.1 Part 2, 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 than EU-Stelara and US-Stelara.

Table 52: Immunogenicity Results in Study CT-P43 1.1 Part 2 (Safety Set)

Treatment group	N	Anti-Drug antibody (ADA) response rate		NAb (at End of Study)
		Baseline	Treatment-Induced (At end of study)	
CT-P43	80	0	13 (16.3%)	5 (6.3%)
EU-Stelara	82	0	24 (29.3%)	6 (7.3%)
US-Stelara	78	0	34 (43.6%)	9 (11.5%)

Source: Clinical Study Report: CT-P43 1.1 Post-text Table 14.3.6.8

Impact of ADA on PK of study drugs in Study CT-P43 1.1 (Part 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}.

Table 53. Impact of ADA positivity (post-treatment ADA status) on C_{max} and AUC_{0-inf} in Study CT-P43 1.1 Part 2 (PK Set)

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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} (µg/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-inf} (day*µg/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

Source: Clinical study report CT-P43 1.1 Post-text Table 14.2.1.4

14.4.2. Summary of Bioanalytical Method Validation and Performance

Pharmacokinetics

For the PK similarity studies (Study CT-P43 1.1, and Study CT-P 1.2), serum CT-P43, US-Stelara, and EU-Stelara concentrations were measured using a validated Electrochemiluminescence (ECL) assay. The same bioanalytical method was used for analyzing PK samples obtained from the comparative clinical study (Study CT-P43 3.1). Both the bioanalytical method validation entitled “Method Validation for the Quantitative Determination of CT-P43 And Ustekinumab in Human Serum Using An electrochemiluminescence (ECL) Assay”^{16,17} and samples analyses^{18,19,20} for three studies were conducted in (b) (4). This method uses an Electro chemiluminescent (ECL) assay format to measure the concentration of CT-P43 in Human Serum. Standards, quality controls, and test samples are incubated with human recombinant monoclonal antibody HCA210 which has been immobilized on MSD GOLD Streptavidin plates. After incubation, unbound material is washed away. Bound CT-P43 is then incubated with a human recombinant

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¹⁷ \\CDSESUB1\EVSPROD\bla761338\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\pk-study\1353565-pk-vr.pdf

¹⁸ \\CDSESUB1\EVSPROD\bla761338\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\pk-study\1354182-pk-ba.pdf

¹⁹ \\CDSESUB1\EVSPROD\bla761338\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\pk-study\1350053-pk-ba.pdf

²⁰ \\CDSESUB1\EVSPROD\bla761338\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\pk-study\1357273-pk-ba.pdf

monoclonal antibody HCA209 that has been conjugated with Sulfo-tag. Following incubation, unbound antibody is washed away and visualized with MSD Read Buffer T(2X), and read on the MSD plate reader. Table 40 shows the summary of MSD – ECL method validation and performance in quantification of CT-P43, US-Stelara, and EU-Stelara during the method validation. Both the method validation and in-study performance were acceptable.

Table 54. Summary of the bioanalytical method validation and in-study performance for measurement of CT-P43, US-Stelara and EU-Stelara

Bioanalytical method review summary	Method validation for the quantitative determination of CT-P43 and ustekinumab in Human serum using an electrochemiluminescence (ECL) assay																																									
Materials used for calibration curve & concentration	CT-P43, 3000.0, 2500.0, 2000.0, 1000.0, 500.0, 250.0, 125.0, 50.0, *25.0 and 0.0 ng/mL *Anchor point																																									
Validated assay range	25 to 3000 ng/mL																																									
Material used for QCs & concentration	CT-P43, US-Stelara, EU-Stelara: ULOQ: 3000.0 ng/mL High: 2400.0 ng/mL Medium: 600.0 ng/mL Low: 100.0 ng/mL LLOQ: 50.0 ng/mL																																									
Minimum required dilutions (MRDs)	1:20 in Assay Buffer																																									
Source & lot of reagents (LBA)	<table><tr><th>Material</th><th>Manufacturer</th><th>Lot #</th><th>(b) (4) Standard Reference Number</th><th>Storage Temperature</th><th>Expiration/Retest Date</th></tr><tr><td>CT-P43 (93 mg/mL)</td><td>Sponsor supplied</td><td>ONGA02</td><td>04449.01 04449.02</td><td>2-8°C</td><td>September 2020</td></tr><tr><td>CT-P43 (92 mg/mL)</td><td>Sponsor supplied</td><td>ONGA04</td><td>04479.01</td><td>2-8°C</td><td>November 2021</td></tr></table> Originator material: Stelara: (b) (4); standard Reference No.: EU: 04448.xx US: 04465.xx <table><tr><th>Material</th><th>Manufacturer</th><th>Lot #</th><th>(b) (4) Standard Reference Number</th><th>Storage Temperature</th><th>Expiration/Retest Date</th></tr><tr><td>Stelara-EU (91 mg/mL)</td><td>Sponsor supplied</td><td>JFS1VVK</td><td>04448.01</td><td>2-8°C</td><td>May 2022</td></tr><tr><td>Stelara-US (5 mg/mL)</td><td>Sponsor supplied</td><td>ICS1P00.A</td><td>04465.01</td><td>2-8°C</td><td>February 2021</td></tr></table>						Material	Manufacturer	Lot #	(b) (4) Standard Reference Number	Storage Temperature	Expiration/Retest Date	CT-P43 (93 mg/mL)	Sponsor supplied	ONGA02	04449.01 04449.02	2-8°C	September 2020	CT-P43 (92 mg/mL)	Sponsor supplied	ONGA04	04479.01	2-8°C	November 2021	Material	Manufacturer	Lot #	(b) (4) Standard Reference Number	Storage Temperature	Expiration/Retest Date	Stelara-EU (91 mg/mL)	Sponsor supplied	JFS1VVK	04448.01	2-8°C	May 2022	Stelara-US (5 mg/mL)	Sponsor supplied	ICS1P00.A	04465.01	2-8°C	February 2021
Material	Manufacturer	Lot #	(b) (4) Standard Reference Number	Storage Temperature	Expiration/Retest Date																																					
CT-P43 (93 mg/mL)	Sponsor supplied	ONGA02	04449.01 04449.02	2-8°C	September 2020																																					
CT-P43 (92 mg/mL)	Sponsor supplied	ONGA04	04479.01	2-8°C	November 2021																																					
Material	Manufacturer	Lot #	(b) (4) Standard Reference Number	Storage Temperature	Expiration/Retest Date																																					
Stelara-EU (91 mg/mL)	Sponsor supplied	JFS1VVK	04448.01	2-8°C	May 2022																																					
Stelara-US (5 mg/mL)	Sponsor supplied	ICS1P00.A	04465.01	2-8°C	February 2021																																					
Validation Parameters	Method Validation Summary					Acceptability																																				
Calibration Curve Reproducibility	No of standard calibrators from LLOQ to upper limit of quantitation (ULOQ)			10	Yes																																					
Acceptance Criteria: - The inter-assay precision (%CV) for each back-calculated calibration point concentration must be ≤ 20.0% (≤ 25.0% at the LLOQ and ULOQ standard points). - The calculated mean % relative error (%RE) from nominal values of each back calculated standard	The inter-assay precision (%CV) for each back-calculated calibration point concentration			≤ 4.2%	Yes																																					
	The calculated mean %RE) from nominal values of each back-calculated standard concentration point			-4.8% to 5.8%																																						
		%TE			≤10.0%.																																					

concentration point must be $\leq \pm 20.0\%$ ($\leq \pm 25.0\%$ at the LLOQ and ULOQ standard points). • %Total error (Absolute %RE + %CV) should be $\leq 30.0\%$ ($\leq 40.0\%$ at the LLOQ and ULOQ). • At least 75% (a minimum six of non-anchor calibration points) must be deemed acceptable for the validation run to be accepted. • In cases where either the LLOQ and/or ULOQ calibration points are rejected then the batch should be rejected from the validation. • No two consecutive calibration points within the quantifiable range (LLOQ to ULOQ) can be removed.	In all validation assay plates, at least 75% (a minimum six of non-anchor calibration points) were acceptable and therefore all validation assay plates were accepted.		
QCs performance during accuracy & precision Per BMV, • The calculated inter-assay %CV of each QC level should be $\leq 20.0\%$ (or $\leq 25.0\%$ at the LLOQ and ULOQ). • The calculated mean %RE of each QC level should be $\leq \pm 20.0\%$ of the nominal concentration (or $\leq \pm 25.0\%$ at the LLOQ and ULOQ). • %TE should be $\leq 30.0\%$ ($\leq 40.0\%$ at the LLOQ and ULOQ).	Cumulative %RE in 5 QCs CT-P43 -3.1% to 7.2 US-Stelara -3.0% to 6.4% EU Stelara -0.6% to 7.6%		Yes
	Inter-batch %CV CT-P43 4.9% to 14.9% US-Stelara 4.4% to 9.1 EU Stelara 3.3% to 7		Yes
	Percent total error (TE) CT-P43 7.8% to 22.1 US-Stelara 4.8% to 15.5 EU Stelara 7.0% to 15.0		Yes
Selectivity & matrix effect Target Criteria: At least 80% of the LLOQ CT-P43, LLOQ Stelara-EU and LLOQ Stelara-US spiked individuals must measure $\leq \pm 25.0\%$ of the nominal concentration.	No matrix effect observed in normal healthy human serum or disease state serum (plaque psoriasis) lots prepared with CT-P43, US-Stelara, or EU-Stelara at HQC level. However, 90% of the LLOQ CT-P43, spiked non-diseased and diseased individuals generated %RE results $\leq \pm 25.0\%$ of the nominal concentration, ranging between 13.4% and 25.0% for the non-diseased individuals and -4.0% to 12.4% for the diseased individuals. The non-diseased individual that failed to meet the $\leq \pm 25.0\%$ of the nominal concentration criteria yielded a result that was 29.0% from the nominal concentration. The diseased individual that failed to		

	meet the $\leq \pm 25.0\%$ of the nominal concentration yielded a result that was 28.2% from the nominal concentration. Thus, by combining the data obtained with non-diseased and diseased individuals i.e. out of the 20 individuals assessed, 18 out of the 20 individuals, equating to 90%, and meeting the target criteria.	
Hemolysis effect	No effect from hemolysis up to 80% fully lysed whole blood on the quantitation of CT-P43 or Stelara	
Lipemic effect	Visually lipaemic serum had no adverse effects on the assay performance for quantitation of CT-P43 or Stelara	
Dilution linearity & hook effect	150µg/mL of CT-P43, US-Stelara and EU-Stelara diluted 10, 200, 1000-fold. No evidence of prozone effects up to 150µg/mL of CT-P43, US-Stelara and EU-Stelara	
Bench-top/process stability	Up to 22 hours 16 minutes for LQC, and HQC prepared with CT-P43, US-Stelara, and EU-Stelara	
Freeze-Thaw stability	Up to five cycles for LQC, and HQC prepared with CT-P43, US-Stelara and EU-Stelara.	
Long-term storage	Long term stability has been shown for up to 12 months at nominal -80°C and at nominal -20°C	
Parallelism	Not Applicable	
Carry over	Not applicable	
Method Performance in Study CT-P43 1.2²¹		
Assay passing rate	92%	Yes
Standard curve performance	- The mean %RE from target concentration for all calibrator levels: -2.2% to 2.7%. - Cumulative precision (CV%): 2.5 to 3.9%	Yes
QC performance	- Cumulative Accuracy (CV%): 8.3 to 33.7 - Mean RE%: -3.8 to 3.7	Yes
Method reproducibility	Incurred sample reanalysis was performed in 766 samples study samples (10.4% of total sample size) and 92.7% of samples met the pre-specified criteria	Yes
Study sample analysis/ stability	Samples were stored for a maximum of 129 days between sample collection and analysis, which is within the established long-term stability window of 12 months.	
Method Performance in Study CT-P43 3.1²²		
Assay passing rate	93%	
Standard curve performance	- The mean %RE from target concentration for all calibrator levels: -1.8% to 2.1%. - Cumulative precision (CV%): 2.5 to 3.7%	
QC performance	- The mean %RE from target concentration for all calibrator levels: 0.9 to 6.8%. - Cumulative precision (CV%): 5 to 8.1%	
Method reproducibility	Incurred Sample Re-analysis (ISR) was performed on 354 samples which equated to 10.2% of the total	

²¹ \\CDSESUB1\EVSPROD\bla761338\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\pk-study\1357273-pk-ba.pdf

²² \\CDSESUB1\EVSPROD\bla761338\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\pk-study\1350053-pk-ba.pdf

	number of samples analysed. 98% of samples passed the pre-specified acceptance criteria.	
Study sample analysis/ stability	Samples were stored for a maximum of 212 days between sample collection and analysis, which is within the established long-term stability window of 12 months	
Method Performance in Study CT-P43 1.1²³		
Assay passing rate	92%	Yes
Standard curve performance	- The mean %RE from target concentration for all calibrator levels: -1.9% to 1.9%. - Cumulative precision (CV%): 2.4 to 3.7%	Yes
QC performance	- The mean %RE from target concentration for all calibrator levels: 2 to 8%. - Cumulative precision (CV%): 5.9 to 9%	Yes
Method reproducibility	ISR was performed on 602 samples which equated to 10.0% of the total number of samples analyzed for this study. In total, ISR passed the acceptance criterion with 96.0% of the reanalyzed samples being within $\pm 30\%$ of the mean result (578 out of 602 samples).	Yes
Study sample analysis/ stability	Samples were stored for a maximum of 577 days between sample collection and analysis, which was not within the established long-term stability window of 12 months	No

Source: BLA761338; Module 5.3.1.4

14.4.3. Other Clinical Pharmacology Information

Summary of OSIS inspection outcome at bioanalytical site at (b) (4)

It is of note that an OSIS inspection was conducted at the bioanalytical site. Following observations and conclusion were reported in OSIS inspection memorandum.



²³ \\CDSESUB1\EVSPROD\bla761338\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\pk-study\1354182-pk-ba.pdf

²⁴ \\CDSESUB1\EVSPROD\bla761338\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\pk-study\1347822-pk-vr.pdf

²⁵ \\CDSESUB1\EVSPROD\bla761338\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\pk-study\1347822-pk-vr.pdf

(b) (4)

OSIS concluded that this observation did not impact the reliability of study results.

- (b) (4)
- Based on the OPQ assessment, immunogenicity assay is acceptable and reliable.

14.5. Clinical Appendices

Table 55 Demographics for CT-P43 1.1 Study

Demographic Characteristics	US-Stelara N=78 Count (%)	EU-Stelara N=98 Count (%)	CT-P43 N=94 Count (%)
Age			
Age 39 or younger	67 (86%)	83 (84.7%)	82 (87.2%)
Age between 40 and 64	11 (14%)	15 (15.3%)	12 (12.8%)
Mean	29	30	28
Std Dev	9.4	9.	8.9
Race			
AMERICAN INDIAN OR ALASKA NATIVE	1 (1.3%)	0 (0.0%)	0 (0.0%)
ASIAN	14 (18%)	11 (11%)	9 (10%)
BLACK OR AFRICAN AMERICAN	3 (3.8%)	3 (3.1%)	4 (4.3%)

²⁶ Page 86; [\\CDSESUB1\EVSPROD\bla761338\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\pk-study\1347822-pk-vr.pdf](#)

²⁷ Page 87; [\\CDSESUB1\EVSPROD\bla761338\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\pk-study\1347822-pk-vr.pdf](#)

²⁸ Page 90; [\\CDSESUB1\EVSPROD\bla761338\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\pk-study\1347822-pk-vr.pdf](#)

²⁹ Page 89; [\\CDSESUB1\EVSPROD\bla761338\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\pk-study\1347822-pk-vr.pdf](#)

Demographic Characteristics	US-Stelara N=78 Count (%)	EU-Stelara N=98 Count (%)	CT-P43 N=94 Count (%)
Age			
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0 (0.0%)	1 (1.0%)	1 (1.1%)
WHITE	53 (68%)	73 (75%)	66 (70%)
OTHER	7 (9.0%)	10 (10.2%)	14 (15%)
Ethnicity			
HISPANIC OR LATINO	1 (1.3%)	4 (4.1%)	4 (4.3%)
NOT HISPANIC OR LATINO	73 (93.6%)	91 (92.9%)	84 (89.4%)
UNKNOWN	4 (5.1%)	3 (3.1%)	6 (6.4%)
Sex			
Male	78 (100%)	98 (100%)	94 (100%)
Country			
New Zealand	78 (100%)	98 (100%)	94 (100%)

Table 56 Demographics for CT-P43 1.2 Study

Demographic Characteristics	US-Stelara N=106 Count (%)	EU-Stelara N=108 Count (%)	CT-P43 N=111 Count (%)
Age			
Age 39 or younger	59 (55.7%)	75 (69.4%)	74 (66.7%)
Age between 40 and 64	47 (44.3%)	33 (30.6%)	37 (33.3%)
Mean	36.48	33.34	34.40
Std Dev	11.20	10.54	10.27
Race			
Asian	106 (100%)	108 (100%)	111 (100%)
Ethnicity			
Not Hispanic or Latino	106 (100%)	108 (100%)	111 (100%)
Country			
Japan	106 (100%)	108 (100%)	111 (100%)

Table 57 Treatment-Emergent Adverse Events for $\geq 2\%$, CT-P43 1.1

Body System or Organ Class Dictionary-Derived Term	US-Stelara (N= 78)	EU-Stelara (N = 98)	CT-P43 (N=94)
	Count (%)	Count (%)	Count (%)
Injury, poisoning and procedural complications			
Skin abrasion	6 (7.7%)	11 (11.2%)	8 (8.5%)
Skin laceration	5 (6.4%)	4 (4.1%)	7 (7.4%)
Contusion	3 (3.8%)	6 (6.1%)	3 (3.2%)
Ligament sprain	3 (3.8%)	4 (4.1%)	5 (5.3%)
Muscle strain	1 (1.3%)	6 (6.1%)	3 (3.2%)
Sunburn	1 (1.3%)	5 (5.1%)	3 (3.2%)
Arthropod bite	2 (2.6%)	1 (1.0%)	0
Hand fracture	0	0	2 (2.1%)

Body System or Organ Class Dictionary-Derived Term	US-Stelara (N= 78)	EU-Stelara (N = 98)	CT-P43 (N=94)
	Count (%)	Count (%)	Count (%)
Tooth fracture	0	2 (2.0%)	0
Infections and infestations			
Upper respiratory tract infection	19 (24.4%)	23 (23.5%)	15 (16.0%)
Gastroenteritis	1 (1.3%)	8 (8.2%)	4 (4.3%)
Localised infection	0	0	2 (2.1%)
General disorders and administration site conditions			
Injection site reaction	7 (9.0%)	10 (10.2%)	11 (11.7%)
Fatigue	5 (6.4%)	5 (5.1%)	4 (4.3%)
Vessel puncture site bruise	3 (3.8%)	3 (3.1%)	7 (7.4%)
Vessel puncture site pain	1 (1.3%)	1 (1.0%)	2 (2.1%)
Influenza like illness	1 (1.3%)	2 (2.0%)	0
Nervous system disorders			
Headache	11 (14.1%)	19 (19.4%)	20 (21.3%)
Lethargy	2 (2.6%)	0	0
Migraine	0	2 (2.0%)	0
Syncope	0	2 (2.0%)	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	3 (3.8%)	4 (4.1%)	7 (7.4%)
Nasal congestion	4 (5.1%)	5 (5.1%)	1 (1.1%)
Cough	1 (1.3%)	3 (3.1%)	5 (5.3%)
Rhinorrhoea	4 (5.1%)	2 (2.0%)	1 (1.1%)
Throat irritation	2 (2.6%)	2 (2.0%)	1 (1.1%)
Dry throat	2 (2.6%)	1 (1.0%)	1 (1.1%)
Epistaxis	1 (1.3%)	1 (1.0%)	2 (2.1%)
Pleuritic pain	2 (2.6%)	0	0
Gastrointestinal disorders			
Nausea	2 (2.6%)	2 (2.0%)	5 (5.3%)
Diarrhoea	2 (2.6%)	4 (4.1%)	2 (2.1%)
Abdominal discomfort	2 (2.6%)	3 (3.1%)	1 (1.1%)
Toothache	3 (3.8%)	1 (1.0%)	1 (1.1%)
Vomiting	0	2 (2.0%)	3 (3.2%)
Abdominal pain	2 (2.6%)	1 (1.0%)	1 (1.1%)
Abdominal pain lower	0	1 (1.0%)	2 (2.1%)
Dyspepsia	0	2 (2.0%)	0
Musculoskeletal and connective tissue disorders			
Back pain	2 (2.6%)	2 (2.0%)	5 (5.3%)
Musculoskeletal chest pain	2 (2.6%)	2 (2.0%)	1 (1.1%)
Pain in extremity	1 (1.3%)	2 (2.0%)	2 (2.1%)
Arthralgia	1 (1.3%)	0	3 (3.2%)
Neck pain	1 (1.3%)	2 (2.0%)	0
Skin and subcutaneous tissue disorders			
Rash	1 (1.3%)	0	2 (2.1%)
Eczema	0	2 (2.0%)	0
Psychiatric disorders			
Anxiety	2 (2.6%)	1 (1.0%)	0
Cardiac disorders			

Body System or Organ Class Dictionary-Derived Term	US-Stelara (N= 78)	EU-Stelara (N = 98)	CT-P43 (N=94)
	Count (%)	Count (%)	Count (%)
Palpitations	1 (1.3%)	1 (1.0%)	3 (3.2%)
Immune system disorders			
Seasonal allergy	0	1 (1.0%)	3 (3.2%)
Blood and lymphatic system disorders			
Lymphadenopathy	2 (2.6%)	0	0

Table 58 Treatment-Emergent Adverse Events for ≥1%, CT-P43 1.2

Body System or Organ Class Dictionary-Derived Term	US- Stelara N = 106 Count (%)	EU- Stelara N = 108 Count (%)	CT-P43 N = 111 Count (%)
Investigations			
Blood creatine phosphokinase increased	4 (3.8%)	5 (4.6%)	8 (7.2%)
Alanine aminotransferase increased	6 (5.7%)	4 (3.7%)	3 (2.7%)
Aspartate aminotransferase increased	2 (1.9%)	3 (2.8%)	3 (2.7%)
Gamma-glutamyltransferase increased	3 (2.8%)	2 (1.9%)	2 (1.8%)
C-reactive protein increased	1 (0.9%)	0 (0%)	4 (3.6%)
Blood lactate dehydrogenase increased	3 (2.8%)	1 (0.9%)	0 (0%)
Blood triglycerides increased	0 (0%)	2 (1.9%)	2 (1.8%)
Infections and infestations			
Nasopharyngitis	9 (8.5%)	8 (7.4%)	4 (3.6%)
COVID-19	4 (3.8%)	5 (4.6%)	9 (8.1%)
Upper respiratory tract infection	2 (1.9%)	1 (0.9%)	2 (1.8%)
General disorders and administration site conditions			
Injection site reaction	10 (9.4%)	14 (13%)	22 (20%)
Musculoskeletal and connective tissue disorders			
Myalgia	1 (0.9%)	5 (4.6%)	2 (1.8%)
Back pain	2 (1.9%)	2 (1.9%)	1 (0.9%)
Gastrointestinal disorders			
Diarrhoea	2 (1.9%)	2 (1.9%)	2 (1.8%)
Abdominal pain	0 (0%)	3 (2.8%)	1 (0.9%)
Skin and subcutaneous tissue disorders			
Rash	1 (0.9%)	2 (1.9%)	3 (2.7%)
Nervous system disorders			
Headache	0 (0%)	3 (2.8%)	3 (2.7%)
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	0 (0%)	3 (2.8%)	1 (0.9%)

Authors:
Sena Lee, MD, PhD
Clinical Reviewer

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