BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	351(k) BLA
Application Number	761219
Received Date	November 24, 2020
BsUFA Goal Date	November 24, 2021
Division/Office	Division of Rheumatology and Transplant Medicine (DRTM)/Office of Immunology and Inflammation (OII) in collaboration with the Division of Dermatology and Dentistry (DDD/OII) and Division of Gastroenterology (DG/OII)
Review Completion Date	See DARRTS stamped date
Product Code Name	CT-P17
Proposed Nonproprietary Name[1]	adalimumab-aaty
Proposed Proprietary Name[1]	YUFLYMA
Pharmacologic Class	Tumor Necrosis Factor (TNF) blocker
Applicant	Celltrion, Inc.
• **Applicant Proposed Indication(s)**	• Rheumatoid arthritis (RA): reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. • Juvenile idiopathic arthritis (JIA): reducing signs and symptoms of moderately to severely active polyarticular JIA in patients ≥ 2 years of age. • Psoriatic arthritis (PsA):reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA. • Ankylosing spondylitis (AS): reducing signs and symptoms in adult patients with active AS. • Crohn's disease (CD):treatment of moderately to severely active Crohn's disease in adults and pediatric patients ≥ 6 years of age, • Ulcerative colitis (UC):treatment of moderately to severely active ulcerative colitis in adult patients. • Plaque psoriasis (Ps): treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and

[1]Section 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.

	when other systemic therapies are medically less appropriate.
Recommendation on Regulatory Action	Complete Response

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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
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
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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1. Executive Summary

1.1. Product Introduction

Celltrion (also referred to as the "Applicant" in this review) has submitted a biologic license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for CT-P17 as a proposed biosimilar to US-licensed Humira (adalimumab).

CT-P17 is a fully human anti-TNFα IgG1 monoclonal antibody produced in Chinese Hamster Ovary cells using recombinant DNA technology. It is proposed as a biosimilar to US-licensed Humira. CT-P17 binds to TNF-α, blocks its interaction with the p55 and p75 cell surface TNF receptors and neutralizes its biological function.

Celltrion is seeking licensure of CT-P17 for the following indications for which US-Humira has been previously approved[2]:

1) Rheumatoid Arthritis (RA):
   YUFLYMA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. YUFLYMA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).
2) Juvenile Idiopathic Arthritis (JIA):
   YUFLYMA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. YUFLYMA can be used alone or in combination with methotrexate.
3) Psoriatic Arthritis (PsA):
   YUFLYMA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. YUFLYMA can be used alone or in combination with non-biologic DMARDs.
4) Ankylosing Spondylitis (AS):
   YUFLYMA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.
5) Crohn's Disease (CD)
   YUFLYMA is indicated for the treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.
6) Ulcerative Colitis (UC):
   YUFLYMA is indicated for the treatment of moderately to severely active ulcerative colitis in adults.
   Limitations of Use

[2] FDA-approved Humira labeling

The effectiveness of YUFLYMA has not been established in patients who have lost response to or were intolerant to TNF blockers *[see Clinical Studies (14.7, 14.8)]*.

7) Plaque Psoriasis (PsO):
YUFLYMA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. YUFLYMA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Warnings and Precautions (5)]*.

Although the Division of Rheumatology and Transplant Medicine (DRTM) 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 Dermatology and Dental (DDD) 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-P17 binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. CT-P17 also lyses surface TNF expressing cells *in vitro* in the presence of complement. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of patients with RA, JIA, PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques.

CT-P17 drug product is a sterile liquid solution with the following proposed presentations:

- Single-dose prefilled auto-injector (YUFLYMA AI)
  40 mg/0.4 mL

- Single-dose prefilled syringe (YUFLYMA PFS)
  40mg/0.4mL

- Single-dose prefilled syringe with safety guard (YUFLYMA PFS-S)
  Injection: 40 mg/0.4 mL

The route of administration, dosage form, and strength of CT-P17 (40mg/mL in the prefilled syringe, auto-injector and in the prefilled syringe with safety guard) are the same as a subset of those approved for US-Humira.

1.4. Inspection of Manufacturing Facilities

FDA's Office of Pharmaceutical Manufacturing Assessment (OPMA) conducted an assessment of the manufacturing facilities for this BLA.

Celltrion, Inc. (FEI 3005241015) is responsible for drug substance (DS) manufacturing. A review of requested manufacturing site records under Section 704(a)(4) (FDASIA Sec. 706) was conducted in lieu of an onsite pre-license inspection (PLI). The Agency requested audit documents for drug substance manufacturing, testing (including comparative analytical assessment), and storage on February 25, 2021 and April 2, 2021. No objectionable issues were identified. The Agency determined that the proposed drug substance manufacturing facility is acceptable to support approval of BLA 761219.

(b) (4) is responsible for the manufacture, secondary packaging, and testing of CT-P17 drug product (DP). A pre-approval inspection was conducted by OPMA from (b) (4) under profile code SVS in support of BLA 761219/0. The current inspection covered the firm's Quality, Production, Materials, Facilities and Equipment, Laboratory Controls, Packaging and Labeling systems, in order to assess the firm's readiness for CT-P17 DP manufacturing. A 7-item Form FDA 483 was issued, with the inspection field recommendation of withhold, pending the firm's adequate response to objectionable conditions. Refer to the FDA Form 483 for a list of the observations. The response to the FDA Form 483 observations was not adequate and the final inspection conclusion was Official Action Indicated (OAI).

The OPMA team recommends that a Complete Response letter be issued to Celltrion outlining the identified inspection deficiencies from the standpoint of facilities assessment. The CDTL and Division Signatory concur with these recommendations.

CDRH has recommended approval of this application with respect to device constituent parts of the combination product. Additional comments will be conveyed in the action letter. The CDTL and Division Signatory concur with these recommendations.

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

Celltrion provided adequate data to establish the scientific bridge to justify the relevance of data generated from the study CT-P17 3.1, which used EU-HUMIRA as the non-U.S.-licensed comparator product, to the assessment of biosimilarity:

The Office of Pharmaceutical Products (OPQ), CDER has determined, and the CDTL and the Division Signatory agree, that based on the data provided by the Applicant, the analytical component of the scientific bridge between CT-P17, U.S.-HUMIRA, and EU-HUMIRA was established.

- The Office of Clinical Pharmacology (OCP) has determined, and CDTL and the Division Signatory agree, that based on the data provided by the Applicant, the PK data establish the PK component of the scientific bridge.

1.6. Biosimilarity Assessment

Table 1. Summary and Assessment of Biosimilarity

Comparative Analytical Studies[3]	
Summary of Evidence	• CT-P17 is highly similar to US-Humira notwithstanding minor differences in clinically inactive components. • CT-P17 prefilled syringes (40 mg/0.4 mL) and autoinjector (40 mg/0.4 mL) are the same strength as that of US-Humira. • The dosage form and route of administration is also the same as that of US-Humira • The analytical component of the scientific bridge between CT-P17, US-Humira, and EU-Humira was established to support the relevance of the data generated from studies using EU-Humira as the comparator to the assessment of biosimilarity.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the product quality assessment.
Animal/Nonclinical Studies	
Summary of Evidence	• A 1-month monkey toxicity study that compared CT-P17 and EU-Humira was submitted. Given the scientific bridge was established (based on the analytical and PK comparisons) between CT-P17, US-Humira, and EU-Humira to justify the relevance of data generated with EU-Humira as the comparator, the information in the pharmacology/toxicology assessment support the demonstration of biosimilarity.

[3]Refer to the Comparative Analytical Assessment (CAA) Chapter of the IQA for additional information regarding comparative analytical data.

Assessment of Residual Uncertainties	• There are no residual uncertainties from the pharmacology/toxicology assessment.
Clinical Studies	
Clinical Pharmacology Studies	
Summary of Evidence	• A PK similarity study (Study CT-P17 1.1) evaluated PK similarity between CT-P17, EU-Humira and US-Humira in healthy subjects • PK similarity has been demonstrated between CT-P17 and US-Humira, and supports a demonstration of no clinically meaningful differences between CT-P17 and US-Humira. • PK similarity between CT-P17, EU-Humira, and US-Humira provides the PK component of the scientific bridge to support the relevance of comparative data generated using EU-Humira to the assessment of biosimilarity. • Similar incidence of ADA and Nab formation was observed between CT-P17, EU-Humira and US-Humira in healthy subjects (Study CT-P17 1.1) and between CT-P17 and EU-Humira in patients with RA(Study CT-P17 3.1), including following the single transition from EU-Humira to CT-P17. Given the scientific bridge was established (based on the analytical and PK comparisons) between CT-P17, US-Humira, and EU-Humira to justify the relevance of data generated with EU-Humira as the comparator, these collective immunogenicity results supports the assessment of no clinically meaningful differences between CT-P17 and US-Humira. • PK of CT-P17 administered using PFS and AI was comparable (Study CT-P17 1.3).
Assessment of Residual Uncertainties	• There are no clinical pharmacology residual uncertainties regarding PK and immunogenicity assessments.
Additional Clinical Studies	

Summary of Evidence	• In Study CT-P17 3.1, there were no meaningful differences in terms of safety and efficacy between CT-P17 and EU-Humira. The frequency of treatment emergent adverse events, serious adverse events, and events leading to discontinuation of study drug had no meaningful differences between the treatment arms. • Given the scientific bridge was established (based on the analytical and PK comparisons) between CT-P17, US-Humira, and EU-Humira to justify the relevance of the data generated with EU-Humira as the comparator, the collective evidence from submitted clinical studies, including the comparative clinical study CT-P17 3.1 in patients with rheumatoid arthritis (RA), supports a demonstration of no clinically meaningful differences between CT-P17 and US-Humira.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical or statistical perspective regarding the demonstration of no clinically meaningful differences between CT-P17 and US-Humira.
Extrapolation	
Summary of Evidence	• DG, DDD 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 submitted, including clinical data from the studied population (RA), to support licensure of CT-P17, as a biosimilar, under section 351(k) of the PHS Act, for the following indications for which US-licensed Humira has been previously approved: • Treatment of inflammatory bowel disease indications [ulcerative colitis (in adults) and Crohn's disease (in adults and in pediatric patients 6 years of age and older)] • Treatment of moderate to severe plaque psoriasis • Treatment of juvenile idiopathic arthritis in patients 2 years of age and older • Treatment of psoriatic arthritis • Treatment of ankylosing spondylitis

Assessment of Residual Uncertainties	• There were no residual uncertainties regarding the extrapolation of data and information to support licensure of CT-P17 as a biosimilar to US-Humira for the above indications.

1.7. Conclusions on Approvability

In considering the totality of the evidence, the data submitted by the Applicant show that CT-P17 is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between CT-P17 and US-Humira in terms of the safety, purity, and potency of the product. The Applicant also provided adequate scientific justification for extrapolation of data and information to support licensure of CT-P17 for JIA in patients 2 years and older, PsA, AS, PsO, CD (in adults and pediatric patients 6 years of age and older), and UC. The information submitted by the Applicant demonstrates that CT-P17 is biosimilar to US-Humira for each of the following indications for which US-Humira is currently licensed and the Applicant is seeking licensure of CT-P17: RA, JIA in patients 2 years and older, PsA, AS, CD (in adults and pediatric patients 6 years of age and older), and UC (in adults) and should be licensed.

However, data submitted in this application are not sufficient to support a conclusion that the manufacture of CT-P17 is well-controlled and will lead to a product that is safe, pure and potent. Therefore, the FDA review teams 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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Cross-Discipline Team Leader (CDTL)

2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

Table 2.. Presubmission Regulatory History Related to Submission.

Date of FDA Meeting	Meeting Type and Summary of Topics of Addressed	Date and Sequence Number of Related to Correspondence Submitted for IND 135944
October 23, 2017	BPD Type 2 Meeting: to discuss development of CT-P17	Briefing Document submitted on July 7, 2017. FDA provided

	as proposed biosimilar to US-licensed Humira.	official meeting minutes dated November 22, 2017.
July 30, 2018	BPD Type 2 Meeting: to reach an agreement with the Agency that the quality and clinical programs proposed for the development of CT-P17 are adequate to support the quality, safety and efficacy of CT-P17 as a biosimilar to US-licensed Humira.	Briefing Document submitted on March 29, 2018. FDA provided official meeting minutes dated October 26, 2018.
September 18, 2019	BPD Type 2 Meeting: to seek advice on the proposed quality development program of CT-P17 as a biosimilar to US-licensed Humira.	Briefing Document submitted on August 30, 2019. FDA provided official meeting minutes dated November 27, 2019 and additional meeting minutes dated February 24, 2020 from the device perspective.
March 16, 2020	BPD Type 2 Meeting: to provide (b) (4)	Briefing Document submitted on March 4, 2020. FDA provided official meeting minutes dated June 17, 2020.
June 30, 2020	BPD Type 2 Meeting: to seek feedback on the proposed development program for supporting registration of CT-P17, as a biosimilar product to US-licensed Humira. BPD Type 4 Meeting: to seek feedback on the format and content of future BLA submission under section 351(k) of the Public Health Act.	Briefing Document submitted on June 9, 2020. FDA provided official meeting minutes dated September 11, 2020. Briefing Document submitted on June 9, 2020. FDA provided official meeting minutes dated September 11, 2020.
Source: Applicant's CTD Module 1, Section 1.6.3, Page 1, Table 1.6.3-1; BPD: biologic product deviation reporting		

2.2. Studies Submitted by the Applicant

Refer to the Comparative Analytical Assessment (CAA) Chapter of the IQA for additional information regarding comparative analytical data.

Table 3. Animal Studies Submitted

Study Title	Study Number	Species	Number Per Treatment Arm	Study Duration	Route of administration/Dose
Animal Studies					
A 28-Day repeat-dose subcutaneous toxicity study in cynomolgus monkeys with CT-P17 and EU-Humira	*1878-030*	*Cynomolgus Monkey*	*3/sex/group*	*28 Days*	*Subcutaneous; CT-P17: 0, 32, 157 mg/kg/week EU-Humira: 0, 32, 157 mg/kg/week*
-					

Table 4. Overview of CT-P17 Clinical Development Program

Study Identity	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Studies				
CT-P17 1.1 (PK similarity study)	**Primary:** To demonstrate the PK similarity in terms of Cmax, AUC0-inf, and AUC0-last over 71 days **Secondary:** To evaluate the additional PK parameters, safety, and immunogenicity over 71 days	Phase 1, randomized, double-blind, three arm, parallel group, single-dose study in healthy male and female subjects	Healthy subjects	40 mg/0.4 ml (100 mg/mL), a single PFS SC injection of study drug **Randomized: 312** • CT-P17: 103 • EU-Humira: 106 • US-Humira: 103
CT-P17 1.2 ("Pilot" Study)	**Primary:** To evaluate safety in terms of TEAEs over 120 days **Secondary:** To evaluate the PK parameters and additional safety including immunogenicity over 120 days	Phase 1, randomized double-blind, two- arm, parallel group, single-dose study in healthy subjects	Healthy subjects	40 mg/0.4 ml (100 mg/mL), a single PFS SC injection of study drug **Randomized: 30** • CT-P17: 15 • EU-Humira: 15
Comparative Clinical Study				
CT-P17 3.1 (Comparative efficacy and safety study)	**Primary**: To demonstrate efficacy similarity as determined by clinical response according to ACR20 at Week 24. **Secondary**: To evaluate additional efficacy, PK, PD, usability and overall	Phase 3, randomized, active-controlled, double-blind, co-administered with MTX in patients with moderate to severe active rheumatoid arthritis	Rheumatoid arthritis subjects receiving concomitant methotrexate	40 mg/0.4 mL (100 mg/mL) by PFS SC injection of study drug every other week Randomized: • CT-P17: N=324 • EU-Humira: N=324 Co-administered with methotrexate (12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or parenteral

Study Identity	Study Objective	Study Design	Study Population	Treatment Groups
				[intramuscular or subcutaneous]) and folic acid (≥5 mg/week, oral)
Clinical Studies Supporting Device Development				
CT-P17 1.3 (PK study between AI and PFS)	**Primary**: To demonstrate the PK similarity between CT-P17 AI and CT-P17 PFS in terms of AUC0-inf, AUC0-last and Cmax over 71 days **Secondary:** To evaluate the additional PK parameters, safety, and immunogenicity over 71 days	Phase 1, randomized, open-label, two-arm, parallel group, single-dose study in male and female healthy subjects	Healthy subjects	40 mg/0.4 ml (100 mg/mL), a single SC injection of CT-P17 via AI or PFS Randomized: 193 PFS: 95 AI: 98
CT-P17 3.2 (AI usability study)	**Primary:** To evaluate usability of CT-P17 AI assessed by patients at Week 4. **Secondary:** To evaluate change in usability assessed by patients and observers over time up to Week 24. To evaluate overall safety and efficacy over 24 weeks.	Phase 3, open-label, single-arm, multiple dose study in patients with moderate to severe active rheumatoid arthritis	Rheumatoid arthritis subjects receiving concomitant methotrexate	40 mg/0.4 mL (100 mg/mL) by AI SC injection of CT-P17 every other week Co-administered with MTX (12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose) and folic acid (≥5 mg/week, oral). **Randomized:** 62

Source: Applicant's CTD Module 2, Section 2.5, Page 14, Table 2.5-1; PK: pharmacokinetic; AI: auto-injector; PFS: pre-filled syringe

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3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

Adalimumab-aaty (CT-P17) is a recombinant human IgG1 monoclonal antibody manufactured in Chinese Hamster Ovary (CHO) cells. CT-P17 is composed of two light chains (214 amino acid residues each) linked by C-terminal disulfide bonds to two heavy chain (451 amino acid residue each). The total molecular weight of CT-P17 is 148 kilodaltons. The complementarity-determining (CDR) region of CT-P17 facilitates binding to human tumor necrosis factor α (hTNFα). CT-P17 harbors one N-linked glycosylation site (Asn301) in the CH2 domain of the heavy chain which facilitates Fc-effector function. The overall control strategy for CT-P17 manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The manufacturing control strategy coupled with in-process controls, release and stability testing ensures process consistency, and drug substance and drug product that have appropriate quality and are free of adventitious agents.

CT-P17 drug product is manufactured to have the same strength, dosage form and route of administration as the 40 mg/0.4 mL strength of US-licensed Humira in a single-dose prefilled syringe (PFS), PFS assembled with a safety guard (PFS-S), and PFS assembled with an autoinjector (AI). Celltrion, Inc. performed a three-way pairwise comparative analytical assessment (CAA) of CT-P17, US-licensed Humira and EU-approved Humira to establish the analytical component of the scientific bridge to support the relevance of the data generated from clinical studies using EU-approved Humira as a comparator. The CAA results support the demonstration that CT-P17 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components, and the establishment of the analytical component of the scientific bridge. The proposed presentations of CT-P17 (i.e., 40 mg/0.4 mL in single-use PFS, AI and PFS-S) have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as US-licensed Humira (40 mg/0.4 mL). The strength of each CT-P17 presentation is the same as that of US-licensed Humira.

The Office of Pharmaceutical Quality (OPQ), CDER, has completed review of BLA 761219 for Yuflyma (adalimumab-aaty) manufactured by Celltrion, Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of Yuflyma is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life.

The Division of Biotechnology Manufacturing (DBM), Office of Pharmaceutical Manufacturing Assessment (OPMA), OPQ is recommending that a Complete Response letter be issued to Celltrion Inc., to outline the deficiencies and the information and data that will be required to support approval. Sufficient facility and equipment controls are not in place to prevent contamination of and by the application product. Full-scale process performance qualification studies attempted and failed before the PLI, which

demonstrate that the process is not under control. The CDTL and Division Signatory agree with this assessment and the recommendation for a Complete Response.

3.2. Devices

The CT-P17 40mg/0.4ml is filled as either a single-dose, auto-injector (AI), as a single-dose prefilled syringe with safety guard (PFS-S), or a single-dose prefilled syringe (PFS). Enclosed within the auto-injector is a single-dose prefilled syringe.

3.2.1. Center for Devices and Radiological Health (CDRH)

CDRH recommends approval based on assessment of device constituent parts of the combination product. Additional comments will be conveyed in the action letter. Also, refer to the full CDRH OEPQ review.

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

DMEPA reviewed a human factors (HF) validation study for CT-P17 40mg/0.4mL combination product with a single-dose prefilled autoinjector (AI), a single-dose prefilled syringe (PFS), and a single-dose prefilled syringe with safety guard (PFS-S) device constitute parts, and had the following review conclusions:

- The results of the human factors (HF) validation studies support a demonstration that representative users can use the products, as designed, safely and effectively as a biosimilar to US-licensed Humira. Additionally, DMEPA's evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors.

- Considering the totality of the information provided between the proposed CT-P17 40 mg/0.4 mL PFS and the US-licensed Humira 40 mg/0.4 mL PFS, DMEPA agrees with the Applicant's determination that they do not need to submit the results of a human factors (HF) validation study for adolescent patients as part of the marketing application. DMEPA noted that the labeling should not include injections sites not listed for the reference product US-licensed Humira.

In view of the recommendation for a Complete Response, final labeling recommendations will be deferred until the next review cycle, if applicable. For the full DMEPA review, refer to the report in DARRTS on 11/23/2021.

3.3. Office of Study Integrity and Surveillance (OSIS)

The Office of Regulatory Affairs (ORA) inspected (b) (4) . The inspection was conducted under the following submission: (b) (4) The final classification for the inspection was No Action Indicated (NAI). OSIS noted that the previously inspected study under (b) (4) was conducted within 1.5 years of the current study under BLA 761219.

OSIS conducted a Remote Record Review (RRR) for (b) (4) in (b) (4) which falls within the surveillance interval. The RRR was conducted under the following submissions: (b) (4) Although OSIS observed objectionable findings that impacted the reliability of some study data for the analytical portion of studies (b) (4) OSIS recommend that all PK and NAb data be accepted.

Therefore, OSIS concluded based on the rationale described above, inspections are not warranted at this time.

3.4. Office of Scientific Investigations (OSI)

The following clinical study site was selected from the comparative clinical study CT-P17 3.1 for inspection by CDER Office of Scientific Investigations (OSI).

- Site 2516 (Dr. Rafal Wojciechowski, Bydgoszcz, Kujawsko-Pomorskie, Poland): enrolled n=52

This site was selected for inspection based on the high ACR20 response rate at Week 24 (100% in each arm), and relatively large site size without any unusual discontinuation/termination or protocol violation rate. The consult request noted that an analysis comparing CT-P17 vs EU-approved Humira, excluding the site, and the resulting 90% confidence interval was (-5.77%, 5.26%) which falls within the equivalence margin of (-12% to 15%) of the noninferiority study, and thus the primary efficacy result will not be affected.

This request for inspection was marked as non-mission critical. The consult request form noted the following:

> "The COVID-19 global pandemic has significantly limited our ability to conduct on-site Good Clinical Practice (GCP) inspections. Inspections in support of applications not deemed mission critical will be prioritized to proceed when existing travel restrictions are lifted or alternative approaches to onsite inspections are established, if this is feasible prior to the user fee goal date."

The inspection was cancelled as per an email from OSI dated September 8, 2021. They noted that they were not able to get approval for the planned inspection on September 20 to 24, 2021, and that the Office of Regulatory Affairs (ORA) is still limiting foreign

assignments to mission critical applications only; the email noted concerns with the COVID-19 delta variant.

The clinical reviewer confirmed in an email dated September 12, 2021, that the canceled inspection will not impact the review of the application. The clinical reviewer also performed additional analyses to evaluate whether the primary analysis result has been driven by the site. The primary analysis excluding the site revealed that the prespecified similarity margin of (-12%, 15%) was still met for the primary endpoint. Based on the additional analyses, the suspected site did not appear to have impacted the primary analysis result of therapeutic equivalence between CT-P17 and EU-approved Humira. Refer to Section 6.2.1 for more details.

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4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

There were two pre-IND meetings with the applicant on November of 2017 and October of 2018 prior to the submission of the IND on April of 2019. At the November 2017 meeting, the Agency agreed that the ongoing 4-week repeat-dose toxicology study in monkeys with CT-P17 and EU-Humira could be used to support the clinical development of CT-P17and stated that the CT-P17 drug product used in clinical studies should be adequately linked to CT-P17 lots used in nonclinical studies by comparability studies which include both functional and bioanalytical methodologies. In the opening IND 135944, the applicant provided primary pharmacodynamics data comparing CT-P17 100 mg/mL and US-licensed Humira 100 mg/mL; and a 28-Day repeat-dose toxicity study with CT-P17 50 mg/mL and EU-approved Humira 50 mg/mL with once weekly doses up to 32 or 157 mg/kg.
Treatment-related findings in both CT-P17 and EU-Humira were limited to depletion of the germinal centers in the spleen, lymph node (mandibular and/or mesenteric); depletion of lymphoid cortex in thymus; and hemorrhage in the small intestine (duodenum/jejunum). There were no toxicologically relevant differences in animals treated with CT-P17 or EU-approved Humira except for the brain hemorrhage findings in CT-P17 dose groups. Overall, the monkey toxicity study in general and the brain hemorrhage findings in particular are not considered relevant in the context of CT-P17 drug development program because analytical data between CT-P17 50 mg/mL (used in nonclinical studies) and CT-P17 100 mg/mL (used in clinical studies) demonstrate adequate comparability; toxicity profile of CT-P17 100 mg/mL was not compared directly

with 100 mg/mL US-licensed Humira in the monkey study; and additional justifications would not add substantial value to the decision making process.

Systemic exposure to CT-P17 50 mg/mL and EU-approved Humira 50 mg/mL increased in a dose-proportional manner following weekly SC injections.
The systemic exposure and accumulation to CT-P17 and EU-Humira were similar at both doses of 32 mg/kg and 157 mg/kg. Anti-CT-P17 antibodies and anti-EU-Humira antibodies were negative in all treated animals on Days 1 and 29, except 1 female (animal number 106) at 32 mg/kg CT-P17 on Day 29 and 1 female (animal number 110) at 32 mg/kg EU-Humira on Day 29. The presence of positive ADAs in these animals did not affect their serum concentration-time profiles.

Overall, the toxicity and PK/TK profiles of CT-P17 50 mg/mL and EU-approved Humira 50 mg/mL were considered similar.

Given the scientific bridge was established (based on the analytical and PK comparisons) between CT-P17, US-Humira, and EU-Humira to justify the relevance of data generated with EU-Humira as the comparator, the results from the 4 week monkey toxicology study support the demonstration of biosimilarity.

4.1.1. Nonclinical Residual Uncertainties Assessment

There were no nonclinical residual uncertainties.

4.2. Product Information

Product Formulation

CT-P17 drug product will be supplied as a sterile liquid solution intended for subcutaneous (SC) administration in a pre-filled syringe (PFS), PFS with safety guard (PFS-S) or AI (auto-injector) to deliver 40 mg antibody per 0.4 mL solution at a concentration of 100 mg/mL. The excipients in the drug product include 0.06 mg acetic acid, (b) (4) mg sodium acetate (b) (4) 7.51 mg glycine, 0.40 mg polysorbate 80 and qs to 0.4 mL water for injection (Table 5).

Table 5. Composition of the CT-P17 Drug Product Solution (For all 3 proposed devices (PFS, PFS-S, and AI))

Ingredient	Nominal quantity/syringe	Function	Grade
CT-P17	40 mg	Active ingredient	In-house
Acetic acid	0.06 mg	(b) (4)	USP/Ph. Eur.
Sodium acetate (b) (4)	(b) (4) mg		USP/Ph. Eur.
Glycine	7.51 mg		USP/Ph. Eur.
Polysorbate 80	0.40 mg		NF/Ph. Eur.

Ingredient	Nominal quantity/syringe	Function	Grade
Water for Injection	QS to 0.4 mL	(b) (4)	USP/Ph. Eur.

USP: United States Pharmacopoeia, NF: National Formulary, Ph. Eur.: European Pharmacopoeia

Comments on Excipients

Some differences were noted in the compostions of commercial formulation of CT-P17 and US-licensed Humira (see table below). CT-P17 consists of glycine (b) (4) and acetic acid and sodium acetate (b) (4). In contrast, US-Humira has mannitol (b) (4) Polysorbate 80 was present at similar concentrations in both CT-P17 and US-Humira formulations. All the excipients were of compendial grade and their quality standards met the current version of the USP, NF, Ph. Eur. None of the excipients used in CT-P17 were of human or animal origin. Excipients are within the ranges that are found in the inactive ingredient database.

Table 6. Comparison of Excipients in CT-P17 100 mg/mL and US-licensed Humira 100 mg/mL

CT-P17 100 mg/mL (40 mg/0.4 mL)	Nominal quantity/syringe	Humira® 100 mg/mL (40 mg/0.4 mL)	Nominal quantity/syringe	Function
CT-P17	40 mg	adalimumab	40 mg	Active ingredient
Acetic acid	0.06 mg	-	-	(b) (4)
Sodium acetate (b) (4)	(b) (4) mg	-	-	
Glycine	7.51 mg	-	-	
-	-	Mannitol	16.8 mg	
Polysorbate 80	0.40 mg	Polysorbate 80	0.40 mg	
Water for injection	QS to 0.4 mL	Water for injection	QS to 0.4 mL	

Comments on Impurities of Concern

No impurities of toxicological concern were identified. Based on the potential patient exposure levels and a review of available information, the levels of each of the potential leachables from the container closure system are considered qualified from safety perspective and appear to pose no safety concerns to patients.

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5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

Table 7 Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	• A PK similarity study (Study CT-P17 1.1) evaluated PK similarity between CT-P17, EU-Humira and US-Humira in healthy subjects • PK similarity has been demonstrated between CT-P17 and US-Humira, and supports a demonstration of no clinically meaningful differences between CT-P17 and US-Humira. • PK similarity between CT-P17, EU-Humira, and US-Humira provides the PK component of the scientific bridge to support the relevance of comparative data generated using EU-Humira to the assessment of biosimilarity.
Pharmacodynamics	• Not applicable
Immunogenicity	• Similar incidence of ADA and Nab formation was observed between CT-P17, EU-Humira and US-Humira in healthy subjects (Study CT-P17 1.1) and between CT-P17 and EU-Humira in patients with RA(Study CT-P17 3.1), including following the single transition from EU-Humira to CT-P17. Given the scientific bridge was established (based on the analytical and PK comparisons) between CT-P17, US-Humira, and EU-Humira to justify the relevance of data generated with EU-Humira as the comparator, these collective immunogenicity results supports the assessment of no clinically meaningful differences between CT-P17 and US-Humira. • PK of CT-P17 administered using PFS and AI was comparable (Study CT-P17 1.3).
Other (specify)	• PK of CT-P17 administered using PFS and AI was comparable.

The clinical development for CT-P17 included 5 clinical studies (see Table 4 in Section 2.2 for details):

PK similarity was established in the PK similarity study (Study CT-P17 1.1) between CT-P17, EU-Humira, and US-Humira. established the PK component of the scientific bridge to support the relevance of comparative clinical data generated using EU-Humira from Study CT-P17 3.1 to the assessment of biosimilarity.

In the PK similarity study (Study CT-P17 1.1), the 90% CI for the least square (LS) geometric means ratios (LS GMRs) for area under the serum drug concentration-time curve (AUC) from time 0 to infinity ($AUC_{0\text{-}inf}$), AUC from time 0 to the last quantifiable concentration ($AUC_{0\text{-}last}$), and maximum observed drug concentration (C_{max}) were contained within the prespecified criteria of 80 to 125% (Table 8).

Table 8. Summary of statistical analyses for assessment of PK similarity (Study CT-P17 1.1)

Parameter	Geometric Mean* (%CV)			Geometric Mean Ratio** (90% CI)		
	CT-P17 (n=97)	U.S.-Humira (n=93)	EU-Humira (n=100)	CT-P17 vs U.S.-Humira	CT-P17 vs EU-Humira	U.S.-Humira vs EU- Humira
Primary						
$AUC_{0\text{-}inf}$ (µg.h/mL)	2656.5 (43.3)	2469.7 (37.2)	2690.6 (35.1)	105.79 (97.19, 115.16)	98.00 (90.06, 106.63)	92.63 (85.29, 100.61)
$AUC_{0\text{-}last}$ (µg.h/mL)	2372.7 (40.2)	2185.0 (36.4)	2394.7 (36.2)	107.30 (98.29, 117.13)	100.79 (92.42, 109.92)	93.93 (86.08, 102.50)
C_{max} (µg/mL)	3.619 (37.4)	3.556 (33.7)	3.660 (33.4)	101.89 (95.33, 108.89)	100.05 (93.69, 106.85)	98.20 (91.91, 104.92)
Secondary						
T_{max} (h)	167.433 (48.00, 504.08)	166.833 (48.00, 433.22)	144.000 (48.00, 671.35)			

* For T_{max}, median (min, max)
**Presented as percent.
Source: Applicant analysis (CSR CT-P17 1.1 Post-text Table 14.1.2 and Table 14.2.2.1)

The immunogenicity of CT-P17 was comparable to that of US-Humira after a single dose in healthy subjects, EU-Humira after multiple doses in RA patients and after single transition from EU-Humira to CT-P17.

The overall incidence of anti-drug antibody (ADA) formation over the course of the study in healthy subjects was 69.5% and 70.0% for CT-P17 and US-Humira treatment groups, respectively (Study CT-P17 1.1). After multiple 40 mg SC doses, the incidence was also similar (57.9% and 55.5%, respectively) between CT-P17 and EU-Humira in patients

with RA (Study CT-P17 3.1). The overall incidence of neutralizing antibodies (NAb) formation over the course of the study in healthy subjects was 59.3% and 56.7% for CT-P17 and US-Humira, respectively (Study CT-P17 1.1). After multiple SC doses of CT-P17 or EU-Humira, the incidence of NAb formation was also similar (57.1% and 55.2%, respectively) between CT-P17 and EU-Humira in patients with RA (Study CT-P17 3.1). The single transition from EU-Humira to CT-P17 did not result in an increase immunogenicity, with the incidence of ADA and NAb are 45.2% and 45.2%, respectively (Study CT-P17 3.1).

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

Study CT-P17 1.1 adequately demonstrated PK similarity between CT-P17, EU-approved Humira, and US-licensed Humira, establishing the PK component of the scientific bridge.

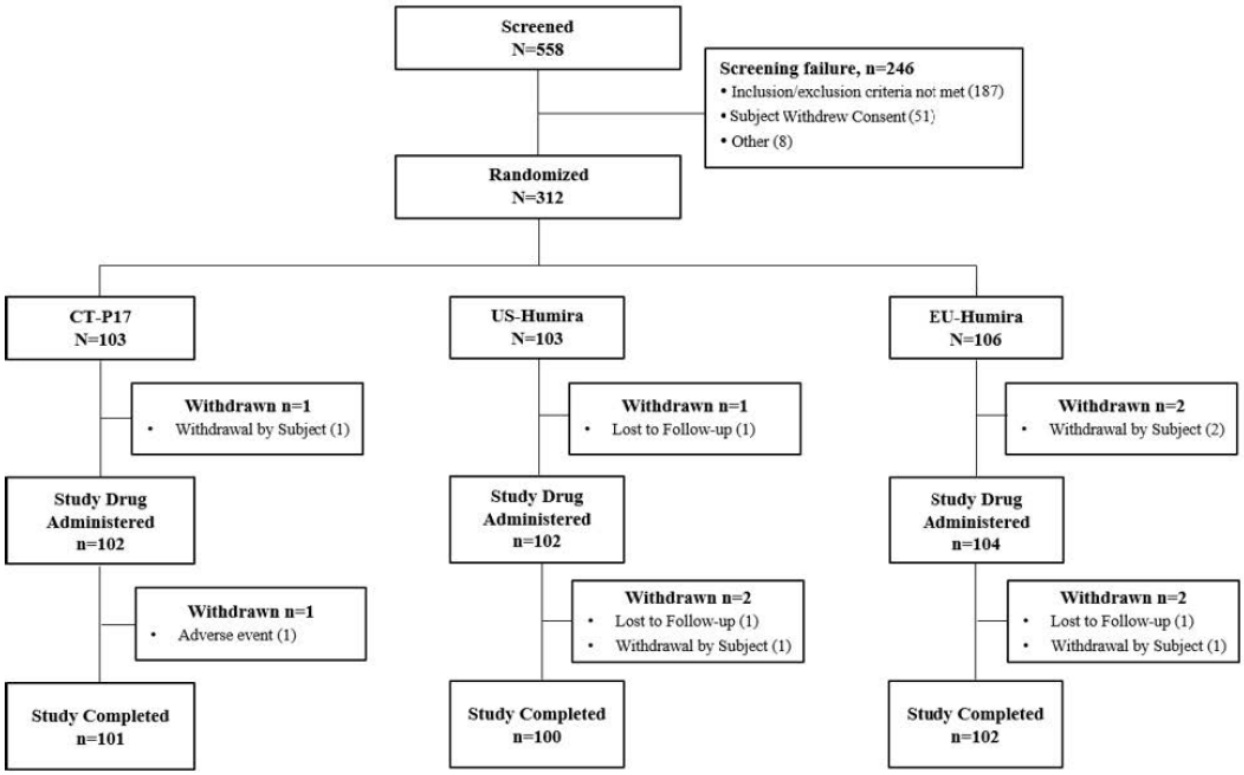
5.3. Human Pharmacokinetic and Pharmacodynamic Studies

5.3.1. Study CT-P17 1.1

Clinical Pharmacology Study Design Features

The PK similarity study comparing CT-P17 PFS, EU-Humira PFS and US-Humira PFS was conducted in healthy subjects (Study CT-P17 1.1). This was a multiple-center study conducted in 10 study centers in Korea. Approximately 312 healthy subjects were planned for dosing as described in the schematic below.

Figure 1 Summary of Subject Disposition



(Source: Figure 10-1 in CSR Study CT-P17 1.1)

Clinical Pharmacology Study Endpoints

In Study CT-P17 1.1, the primary endpoints were C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ to evaluate and compare the PK profiles of CT-P17, EU-Humira, and US-Humira in healthy subjects. Safety, tolerability, and immunogenicity were the secondary endpoints.

Study CT-P17 3.1 was the comparative clinical study in patients with RA. The primary efficacy endpoint was the proportion of patients achieving clinical response (according to the ACR20 criteria) at Week 24, whereas PK (C_{trough}), safety, immunogenicity and other efficacy endpoints (Disease Activity Score 28 (DAS28), ACR20, ACR50, and ACR70, DAS28-CRP, tender and swollen joint counts, CRP, and others) were secondary endpoints. For the choice of efficacy and safety endpoints in Study CT-P17 3.1, see details in Section 6.

The PK primary endpoints in Study CT-P17 1.3 were C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ to compare the PK profiles of CT-P17 administered using PFS and AI in healthy subjects. Safety and tolerability were the secondary endpoints.

Bioanalytical PK Method and Performance

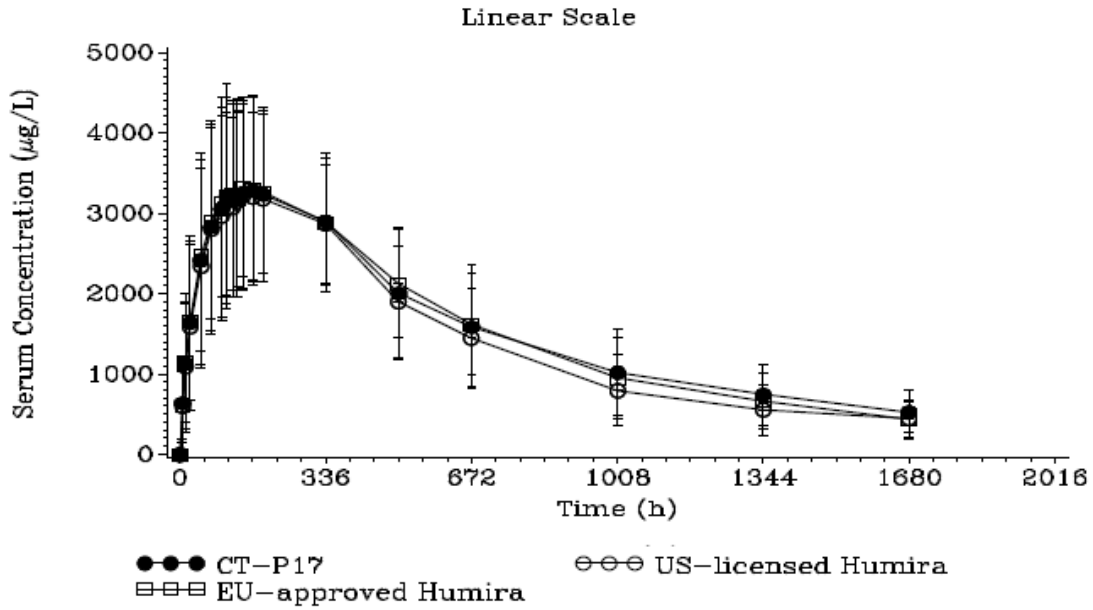
The methodologies used in the analysis of biological samples were sensitive, robust, and fully validated.

The serum concentrations of CT-P17, US-Humira, and EU-Humira were appropriately quantified using a validated electrochemiluminescence assay (ECL) in Study CT-P17 1.1, Study CT-P17 1.3, and Study CT-P17 3.1 (validation reports ICD 809 Project RKAJ8), and Studies CT-P17 1.2 (validation report ICD740 Project RKAJ2). During the method validation, CT-P17, EU-Humira, and US-Humira were used to establish the standard curves, and the accuracy and precision (± 20.0%, ± 25.0% for lower limit of quantitation (LLOQ) and upper limit of quantitation (ULOQ)) was evaluated using CT-P17, US-Humira, and EU-Humira as QC samples. See detailed information about the assay validation in Appendix 13.2.1.

PK Similarity Assessment

PK similarity has been demonstrated among CT-P17, US-Humira, and EU-Humira in the PK similarity Study CT-P17 1.1. In the PK similarity comparison between CT-P17 and US-Humira, the mean serum concentration-time profiles were similar between CT-P17 and US-Humira treatment groups. The 90% CIs for the LS GMRs of C_{max}, AUC_{0-t} and AUC_{0-inf} were all within the pre-defined criteria of 80% –125%. The statistical analysis results of GMR and 90% CI of the primary PK endpoints are listed in Table 8 above. Mean serum concentrations of study drug versus time profiles are presented for the PK population in Figure 2 below.

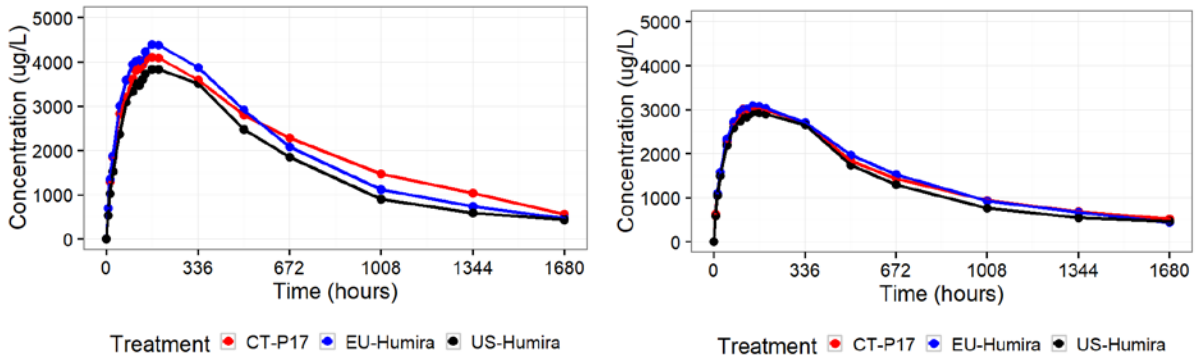
Figure 2 Mean (±SD) Serum Concentrations of Study Drug Versus Time (Linear Scales) (Pharmacokinetic Population)



Abbreviations: EU, European Union; SD, standard deviation; US, United States.
Note. PK concentrations that were BLQ were set to zero prior to study drug administration and missing thereafter.
(Source: Figure 11-1 in CSR Study CT-P17 1.1)

The effect of body weight on PK was evaluate in the figure below. In patients with body weight below and above 60 kg, the mean concentration time profiles were similar between CT-P17, US-Humira, and EU-Humira (Figure 3). This result suggested a similar body weight effect on PK among these three products.

Figure 3 Mean Serum Concentrations of Study Drug Versus Time in Subjects < 60 kg (left) and ≥ 60 kg (right)



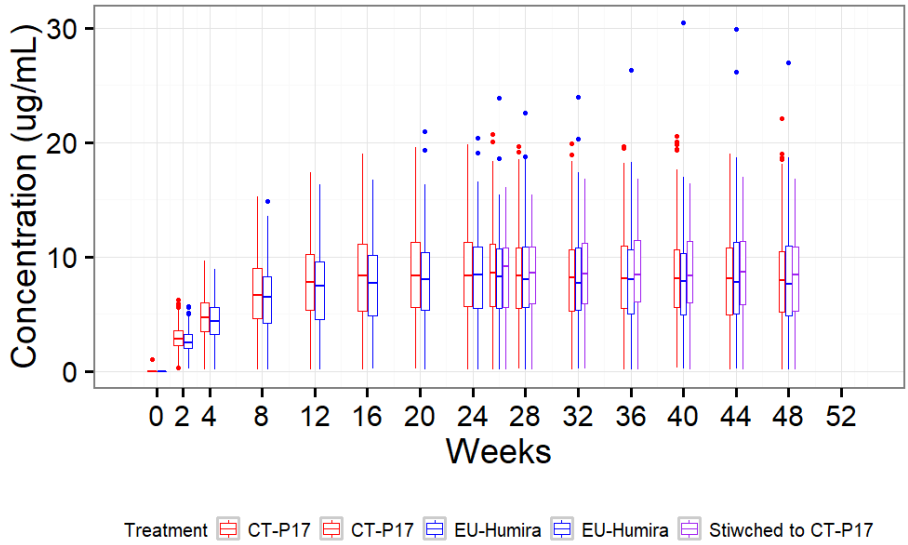
(Source: reviewer's analysis)

5.3.2. Study CT-P17 3.1

Study CT-P17 3.1 was a randomized, active-controlled, double-blind, multicenter, comparative clinical study to evaluate the efficacy, PK, PD, usability (Bulgaria and Poland only), and overall safety including immunogenicity and biomarker of multiple single doses (40 mg) of either CT-P17 or EU-Humira administered by SC injection via pre-filled syringe (PFS) every other week in combination with MTX and folic acid. See section 6 for details of the study design and results.

A comparison of trough concentration (C_{trough}) between CT-P17 and EU-Humira is depicted in Figure 4 below. C_{trough} were similar between CT-P17 and EU-Humira. In patients switched (i.e., who underwent a single transition) from EU-Humira to CT-P17 at Week 24, C_{trough} remained similar as compared to patients who remained on CT-P17 or EU-Humira, respectively.

Figure 4 Comparison of trough concentrations in patients with RA



(source: reviewer's analysis)

In Study CT-P17 3.1, CT-P17 or EU-Humira were administered subcutaneously at different injection sites (the front of the patient's thighs, lower abdomen, or the outer area of the upper arm), and the injection sites should be rotated. Therefore, the effect of injection site on PK might be diluted if there's any. Except Study CT-P17 3.1, in other PK studies, such as Study CT-P17 1.1 and CT-P 1.3, a single dose of study drug was administered subcutaneously in lower abdomen only. Therefore, no head to head comparison of injection site effect on PK was established. In Study CT-P17 3.1, no data suggested a different injection site effect on PK profile of CT-P17 compared to EU-Humira when study drug was administered at different injection sites alternately.

5.3.3. Study CT-P17 1.3

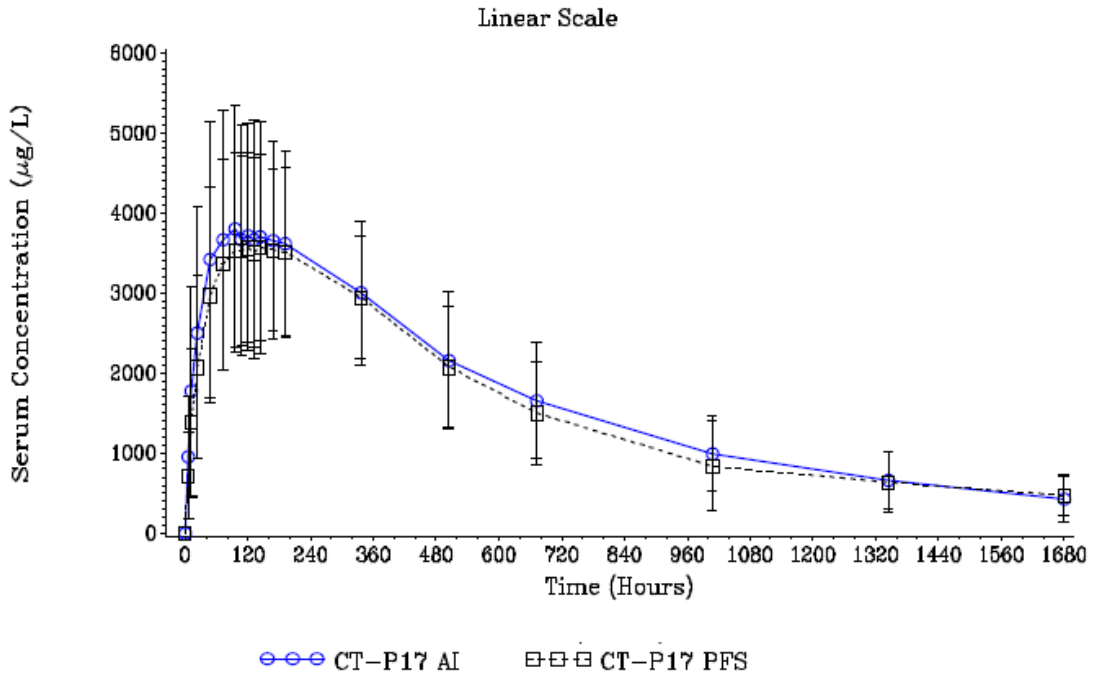
The Applicant conducted a PK comparability study (Study CT-P17 1.3) to support the proposed CT-P17 auto injector (AI) . The PK profiles of CT-P17 using PFS or AI were compared in Study CT-P17 1.3. Study CT-P17 1.3 was a, randomized, open-label, two-arm, parallel group, single-dose study to compare the PK and safety of the AI and PFS of CT-P17 in healthy male and female subjects. A total of 193 healthy subjects were randomized to receive a single dose of 40 mg CT-P17 through SC injection using PFS or AI. The mean serum concentration-time profiles were similar between the PFS and AI (Figure 6). Statistical analysis showed that the AI was comparable to the PFS in terms of all primary PK parameters (AUC_{0-t}, AUC_{0-inf} and C_{max}), as the 90% CIs of the LS GMRs were fully contained within the predefined criteria of 80% to 125% (Table 9).

Table 9 Statistical Analysis of Primary Serum Pharmacokinetic Parameters for CT-P17 (ANCOVA) by Treatment Group (Pharmacokinetic Population)

PK Parameters (Units)	Treatment	Mean (%CV)	Geometric LS Means[1]	Ratio (%) of Geometric LS Means	90% CIs[1]
C_{max} (µg/mL)	CT-P17 AI	4.141 (37.4)	3.801	102.60	(94.08, 111.90)
	CT-P17 PFS	3.908 (32.3)	3.705		
AUC_{0-inf} (h•µg/mL)	CT-P17 AI	2819.5 (33.6)	2606.4	103.64	(93.98, 114.29)
	CT-P17 PFS	2684.5 (38.4)	2514.8		
AUC_{0-last} (h•µg/mL)	CT-P17 AI	2451.3 (44.3)	2110.7	105.36	(91.09, 121.86)
	CT-P17 PFS	2292.9 (44.8)	2003.4		

(Source: Table 2.7.2-12 in Summary of Clinical Pharmacology)

Figure 5 Mean (±SD) Serum Concentrations of CT-P17 (Linear Scale) (Pharmacokinetic Population)



(Source: Figure 11-1 in CSR Study CT-P17 1.1)

5.4. Clinical Immunogenicity Studies

5.4.1. Study CT-P17 3.1

Immunogenicity upon repeated dosing has been evaluated in Study CT-P17 3.1.

Design features of the clinical immunogenicity assessment

Study CT-P17 3.1 was a randomized, double-blind, parallel group, multicenter comparative clinical study in patients with moderate to severe, active RA who were already taking MTX for at least 3 months at a stable dose (10 to 25 mg/week) for a minimum of 8 weeks prior to Screening but who required additional therapy to control their disease. Eligible patients were randomized in a 1:1 ratio to receive either CT-P17 40 mg using PFS (n=366) or EU-Humira 40 mg using PFS (n=362) every other week from Week 0 to Week 24 via SC injection. See section 5.3.2 for additional study design details.

Immunogenicity endpoints

Anti-drug antibodies (ADA) and neutralizing antibodies (NAb) were selected as the immunogenicity endpoints.

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 ADA response to study drug were detected using a validated electrochemiluminescent method (ECL) in Study CT-P17 1.1 (validation reports Project RKAK2) and Study CT-P17 3.1 (validation reports Project RKAK4). The Nab against study drug were detected using a validated MSD-ECL method in Study CT-P17 1.1 (validation reports Project RKAK2) and Study CT-P17 3.1 (validation reports Project RKAK4). Clinical pharmacology defers to the Office of Biopharmaceutics (OBP) for the acceptability of ADA and NAb bioassay methods. Refer to the OBP Immunogenicity review for further details.

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

Blood samples for ADA and NAb assay were collected in Study CT-P17 3.1 from Week 0 to Week 52 as depicted in Figure 4Figure 9 above. ADA and Nab samples were collected with serum PK samples at each timepoint. The last dose, either CT-P17 or EU-Humira, was administered at Week 48. The last ADA and NAb samples were collected at least 4 weeks after the last dose. The sampling time points for ADA and NAb were adequate.

Incidence of ADA and NAb (Provide the incidence of pre-existing antibodies at baseline and the incidence of ADA throughout the study)

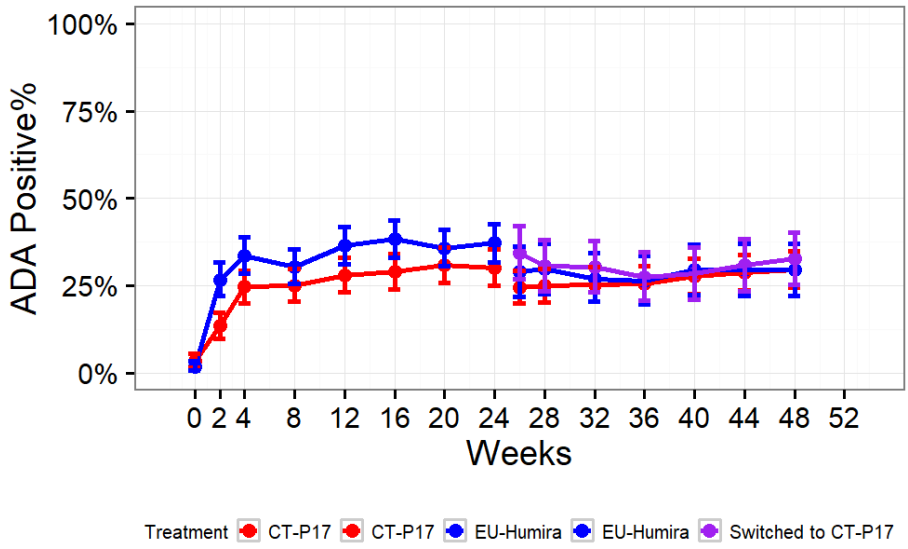
The number and percent of ADA and NAb positive patients are listed in Table 10, and the time course of ADA development is depicted in Figure 6.

Table 10 Immunogenicity results for binding ADA and NAb in Study CT-P17 3.1.

	N	Anti-Drug antibody		NAb
		Baseline	Treatment-Induced	
CT-P17	324	11/324 (3.4%)	93/324 (28.7%)	83/324 (25.6%)
EU-Humira	324	6/324 (1.9%)	116/324 (35.8%)	103/324 (31.8%)

Source: Applicant analysis (CSR CT-P17 3.1 Table 12-28)

Figure 6 Percent of patients who were ADA positive in Study CT-P17 3.1

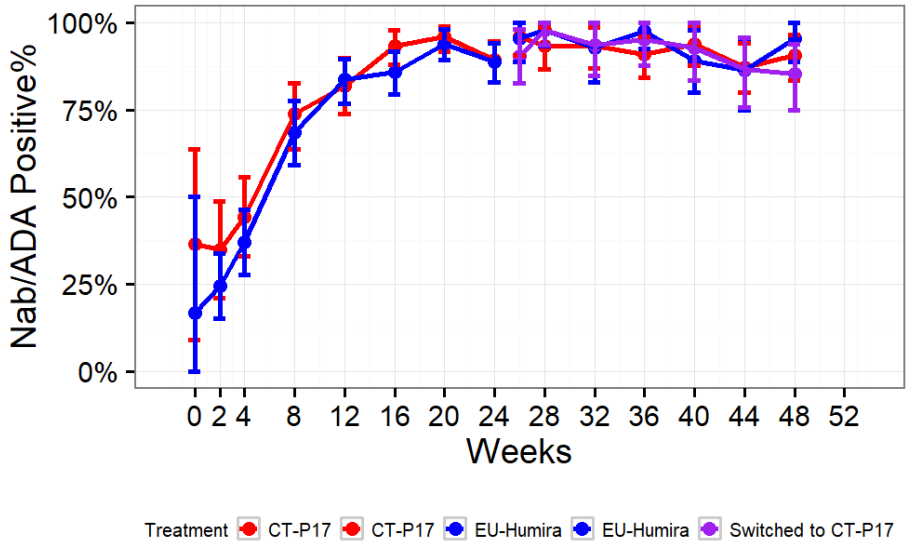


(source: reviewer's analysis)

The ADA positive rate in patients receiving CT-P17 was numerically lower than patients receiving EU-Humira. However, the difference was considered clinically insignificant. See the evaluation of ADA/NAb effect on PK, PD, and efficacy below. In patients switched from EU-Humira to CT-P17 at Week 24, the ADA positive rate remained similar as compared to patients who remained on CT-P17 or EU-Humira, respectively.

In patients who developed ADAs, a time dependent neutralizing antibody development was observed. Almost all ADA positive patients developed NAb after 16 weeks to 20 weeks of treatment. No difference was observed between CT-P17 and EU-Humira. In patients switched from EU-Humira to CT-P17 at Week 24, NAb positive rate remained similar as compared to patients who remained on CT-P17 or EU-Humira, respectively. The time dependent development of NAb and a comparison between CT-P17 and EU-Humira is depicted in Figure 7.

Figure 7 Percent of neutralizing antibody positive patients among ADA positive patients

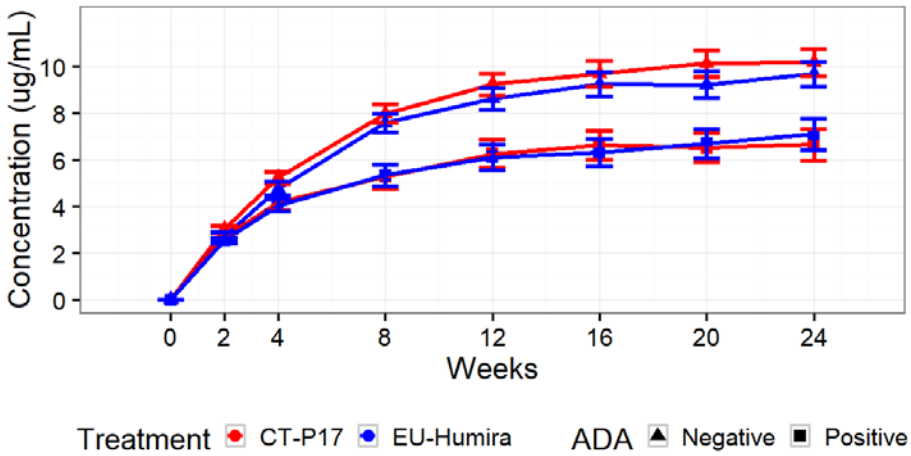


(source: reviewer's analysis)

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

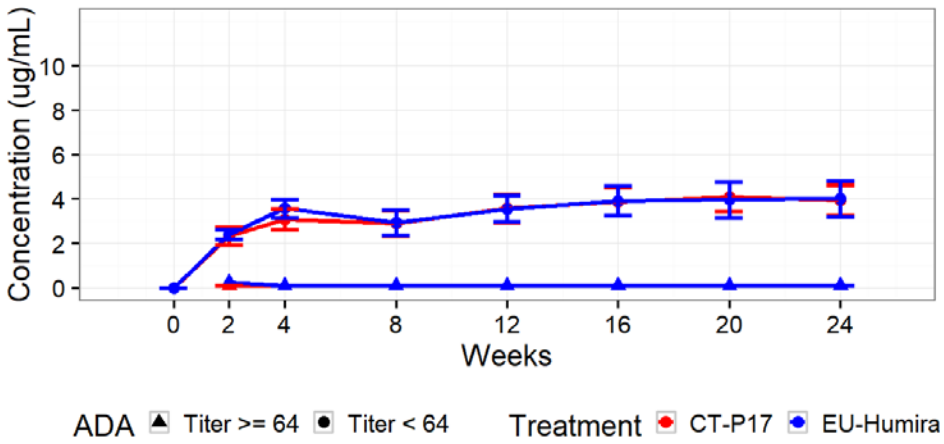
ADA had similar effect on pharmacokinetics of CT-P17 and EU-Humira (Figure 8, Figure 9).

Figure 8 Comparison of anti-drug antibody effect on exposure between CT-P17 and EU-Humira (patient specific)



Patients were considered ADA positive if he/she had at least one positive ADA sample at any time point post treatment
(source: reviewer's analysis)

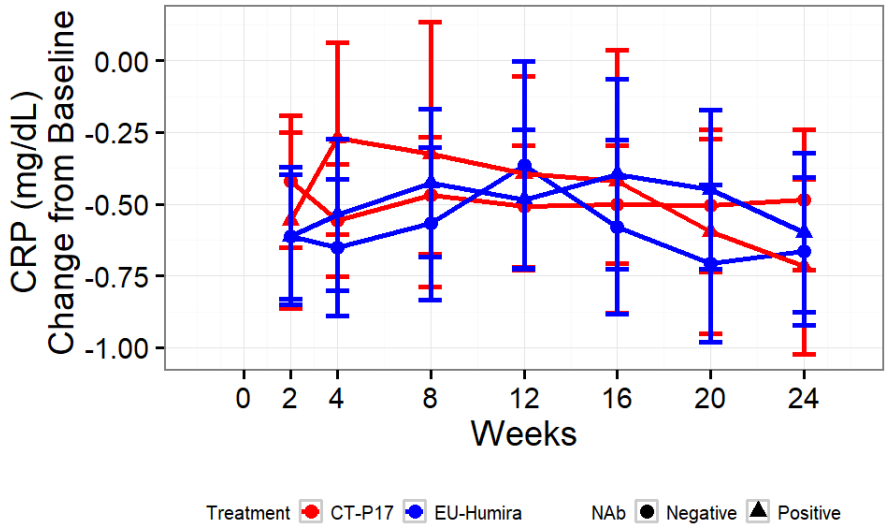
Figure 9 Comparison of high titer (≥ 64) anti-drug antibody effect on exposure between CT-P17 and EU-Humira (time specific)



Patients were considered ADA positive if he/she had a positive ADA sample at the specific time point of interest
(source: reviewer's analysis)

NAb had similar impact on pharmacodynamics (Figure 10) and efficacy (Figure 11).

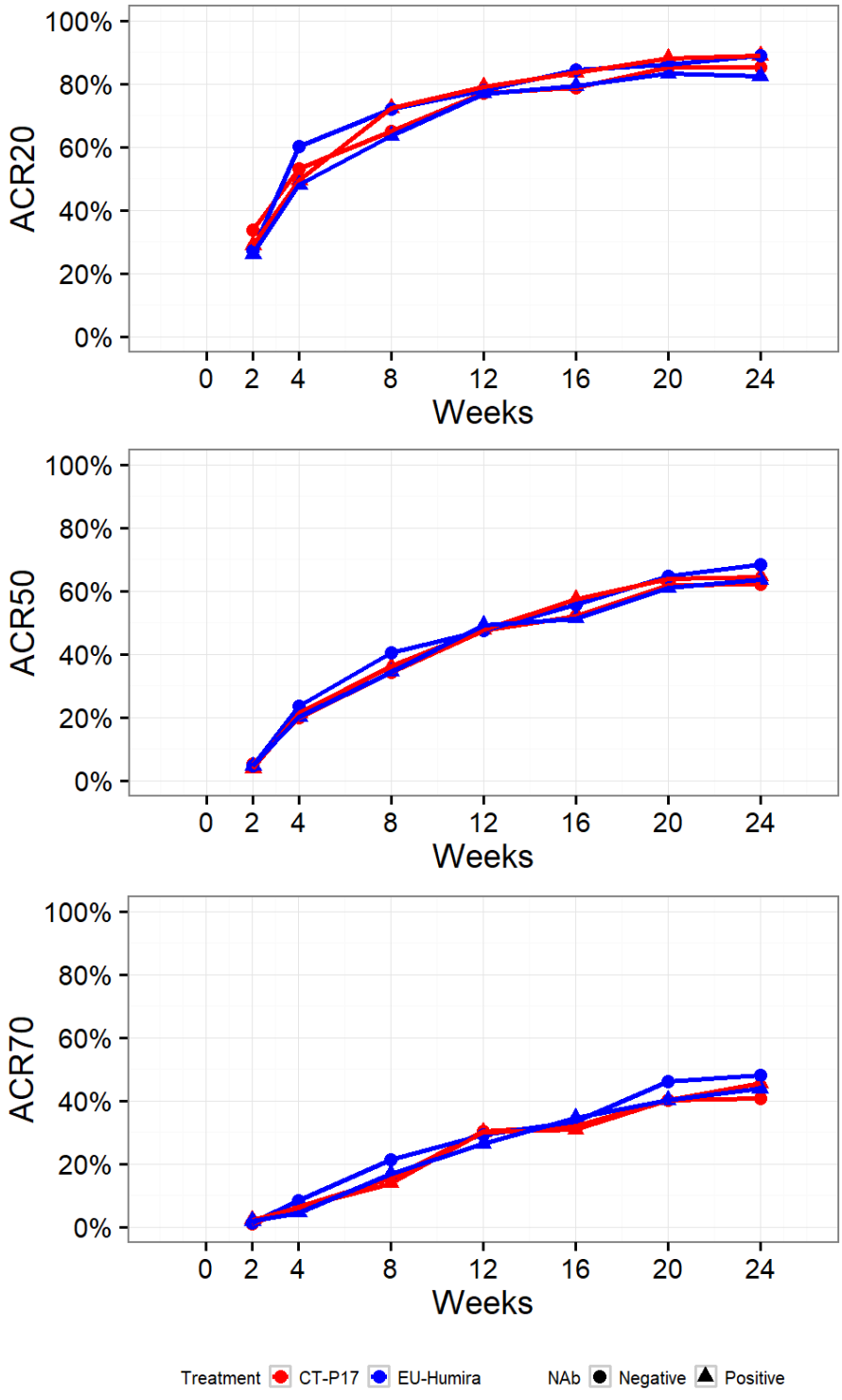
Figure 10 Comparison of neutralizing antibody effect on CRP response between CT-P17 and EU-Humira



(source: reviewer's analysis)

Neutralizing antibody had no effect on clinical efficacy for ACR20, ACR50, and ACR70. The similar ACR responder rates were observed regardless of NAb development (NAb- vs. NAb+) and treatment received (CT-P17 vs. EU-Humira).

Figure 11 Comparison of neutralizing antibody effect on ACR20/ACR50/ACR70 response between CT-P17 and EU-Humira



(source: reviewer's analysis)

5.4.2. Study CT-P17 1.1

In the PK similarity study, Study CT-P17 1.1, ADA positive rates and NAb positive rates in healthy subjects were also similar between CT-P17, US-Humira, and EU-Humira (Table 11).

Table 11 Summary of Immunogenicity Assay (Safety Population)

Immunogenicity Test Visit Result, n (%)	CT-P17 (N=102)	US-Humira (N=102)	EU-Humira (N=104)	Overall (N=308)
ADA				
At least 1 positive after administration[(a)]	**99 (97.1)**	**96 (94.1)**	**99 (95.2)**	**294 (95.5)**
Day 1 (pre-dose)				
Positive	1 (1.0)	1 (1.0)	2 (1.9)	4 (1.3)
Negative	101 (99.0)	101 (99.0)	102 (98.1)	304 (98.7)
Day 15				
Positive	51 (50.0)	53 (52.0)	64 (61.5)	168 (54.5)
Negative	51 (50.0)	45 (44.1)	40 (38.5)	136 (44.2)
Day 29				
Positive	76 (74.5)	78 (76.5)	83 (79.8)	237 (76.9)
Negative	26 (25.5)	21 (20.6)	20 (19.2)	67 (21.8)
Day 57				
Positive	91 (89.2)	91 (89.2)	92 (88.5)	274 (89.0)
Negative	7 (6.9)	9 (8.8)	11 (10.6)	27 (8.8)
EOS				
Positive	97 (95.1)	94 (92.2)	95 (91.3)	286 (92.9)
Negative	4 (3.9)	7 (6.9)	7 (6.7)	18 (5.8)
NAb				
At least 1 positive after administration[(a)]	**79 (77.5)**	**85 (83.3)**	**84 (80.8)**	**248 (80.5)**
Day 1 (pre-dose)				

Immunogenicity Test Visit Result, n (%)	CT-P17 (N=102)	US-Humira (N=102)	EU-Humira (N=104)	Overall (N=308)
Positive	0	0	0	0
Negative	1 (1.0)	1 (1.0)	2 (1.9)	4 (1.3)
Day 15				
Positive	7 (6.9)	9 (8.8)	10 (9.6)	26 (8.4)
Negative	44 (43.1)	44 (43.1)	54 (51.9)	142 (46.1)
Day 29				
Positive	29 (28.4)	30 (29.4)	28 (26.9)	87 (28.2)
Negative	47 (46.1)	48 (47.1)	55 (52.9)	150 (48.7)
Day 57				
Positive	61 (59.8)	73 (71.6)	64 (61.5)	198 (64.3)
Negative	30 (29.4)	18 (17.6)	28 (26.9)	76 (24.7)
EOS				
Positive	73 (71.6)	82 (80.4)	79 (76.0)	234 (76.0)
Negative	24 (23.5)	12 (11.8)	16 (15.4)	52 (16.9)

Abbreviations: ADA, anti-drug antibody; EOS, end of study; EU, European Union; NAb, neutralizing antibody.
US, United States.
Percentages were based on the number of subjects in the safety population per treatment group and overall.
[a] At least 1 positive after administration included scheduled and unscheduled after dose.
(Source: Table 12-8 in CSR CT-P17 1.1)

Overall, all these evaluations of immunogenicity effect on pharmacokinetic, pharmacodynamic (CRP), and efficacy responses support the conclusion of similar immunogenicity response between CT-P17 and EU-Humira.

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6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

Comparative Efficacy:

Study CT-P17 3.1 was a randomized, active-controlled, double-blind, multicenter study designed to evaluate the efficacy, PK, PD, usability (Bulgaria and Poland only), and overall safety including immunogenicity of multiple single 40 mg doses of either CT-P17 or EU-approved Humira (EU-Humira) administered by SC injection via pre-filled syringe

(PFS) every other week (EOW) in combination with MTX and folic acid to subjects with active RA.

The primary endpoint for Study CT-P17 was the proportion of subjects achieving an ACR20 clinical response at Week 24. The 90% confidence interval (CI) for the difference in proportion between the CT-P17 and EU-Humira treatment groups were analyzed with therapeutic similarity of clinical response according to ACR20 criteria being concluded if the 90% CI for the treatment difference was entirely within the limits of -12% to 15% at Week 24.

Approximately 83% of subjects randomized to CT-P17 and 83% of subjects randomized to EU-Humira achieved an ACR20 response (responder) at Week 24, for an estimated proportion difference of 0 (90% CI: -4.98, 4.98). The 90% CI ruled out the similarity margin of (-12%, 15%) proposed by the applicant, which demonstrated therapeutic similarity between the two treatment arms. In a supportive analysis of ACR20 response in the subset of subjects who completed the study and adhered to the protocol (PP population), 87% and 87% responded on CT-P17 and EU-Humira, respectively, for an estimated difference of 0.06% (90% CI: -4.70%, 4.86%) meeting the similarity margin of -12% to 15%. Furthermore, ACR20, ACR50, and ACR70 responses over time, mean changes from baseline in the components of the ACR composite endpoint and the disease activity score (DAS28), and other secondary efficacy endpoint results, showed no obvious differences between CT-P17 and EU-Humira.

Through Week 24 there were 27 subjects who terminated the study before Week 24 (15 [5%] subjects in the CT-P17 treatment arm and 12 [4%] subjects in the EU-Humira treatment arm). The applicant included tipping point analysis to explore the sensitivity of results to violations in assumptions about the missing data. The findings from the tipping point analysis were consistent with the observed results from the primary analysis. Thus, the tipping point results were supportive of the finding of no meaningful differences in efficacy or loss of efficacy between products.

Comparative Safety and Immunogenicity:

The comparative safety evaluation plan of CT-P17 reflected the known safety profile of US-Humira as described in the USPI and other published data. The submitted safety and immunogenicity data from Study CT-P17 3.1, supported by the data from the single-dose PK study, CT-P17 1.1, are adequate to support the demonstration of no clinically meaningful differences in safety and immunogenicity between CT-P17 and US-Humira.

The safety database comprised data from 1,228 subjects from the five clinical studies and included 488 healthy male and female subjects (Studies CT-P17 1.1 and 1.3), 30 healthy male subjects (Study CT-P17 1.2), 648 RA subjects (Study CT-P17 3.1) and 62 RA subjects (Study CT-P17 3.2) who were exposed to at least one dose of CT-P17, US-Humira, or EU-Humira. Of these, 297 healthy subjects and 538 RA subjects were exposed to CT-P17.

The review of safety in this review is focused on Study CT-P17 3.1 given the ability to directly compare the relative safety of CT-P17 to EU-Humira. Due to the design limitations of the remaining four studies (e.g., single dosing), analyses of these safety data will not be presented here; however, review of the safety data was performed for these studies and did not reveal any meaningful differences between CT-P17 when compared to US-Humira or EU-Humira.

The safety database submitted for CT-P17 3.1 included a total of 648 participants who were initially randomized to receive at least one dose of CT-P17 (n=324) or EU-Humira (n=324) through Week 24. For Treatment Period II (at the conclusion of Week 24) 303 subjects initially randomized to CT-P17 were continued on CT-P17, while the subjects initially randomized to EU-Humira were randomized to either continue treatment with EU-Humira (n=153) or to receive treatment with CT-P17 (n=152).

Overall, the data was adequate to provide a reliable descriptive comparison between the products. The safety risks identified are consistent with the known adverse event profile of US-Humira. There were no notable differences between CT-P17 and EU-Humira in treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, adverse events leading to discontinuation, or development of anti-drug antibodies (ADA) between the treatment groups in CT-P17. In addition, a single transition of non-treatment naïve subjects to the proposed biosimilar, i.e., subjects previously treated with EU-Humira to CT-P17, did not result in an increase immunogenicity or clinically significant adverse reactions.

Overall, the collective evidence from the comparative clinical development program supports a demonstration of no clinically meaningful differences between CT-P17 and US-Humira.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the clinical analyses.

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

Of the five clinical studies included in the CT-P17 development program, only Study CT-P17 3.1 was designed to compare the efficacy and safety between CT-P17 and EU-Humira. Studies CT-P17 1.1, 1.2, and 1.3 were single-dose PK studies and CT-P17 3.2 was a single-arm AI usability study. Consequently, only Study CT-P17 3.1 will be used to discuss the comparative efficacy and safety of CT-P17 versus EU-Humira.

6.2.1. Study CT-P 17 3.1

"Protocol CT-P17 3.1: A Randomized, Active-Controlled, Double-Blind, Phase 3 Study to Compare Efficacy and Safety of CT-P17 with EU-approved Humira when Co-

administered with Methotrexate in Patients with Moderate to Severe Active Rheumatoid Arthritis"

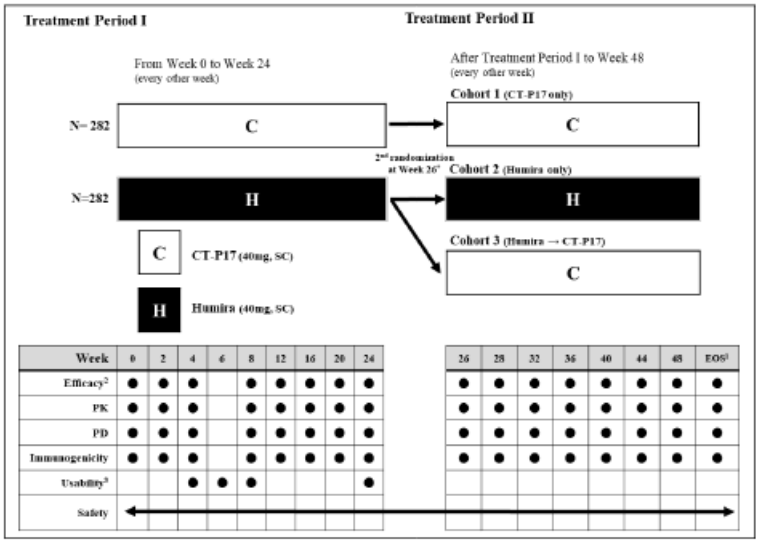
Data and Analysis Quality

There are no concerns regarding data quality and integrity.

Study Design and Endpoints

Study CT-P17 3.1 was a randomized, active-controlled, double-blind, multicenter, comparative clinical study designed to evaluate the efficacy, PK, PD, usability (Bulgaria and Poland only), and overall safety including immunogenicity and biomarker of multiple single 40 mg doses of either CT-P17 or EU-approved Humira (EU-Humira) administered by SC injection via pre-filled syringe (PFS) every other week (EOW) in combination with MTX and folic acid in patients with moderate to severe active rheumatoid arthritis (RA). (Figure 12).

Figure 12. Study Design Overview



Abbreviations: C, CT-P17; EOS, end-of-study; EOW, every other week; H, Humira; N, number of patients; PK, pharmacokinetics; PD, pharmacodynamics; SC, subcutaneous.

* Prior to dosing at Week 26, all patients underwent the second randomization process. Patients who were initially randomly assigned to EU-approved Humira were randomized again in a ratio of 1:1 to either continue EU-approved Humira or undergo transition to CT-P17. All patients who were initially randomly assigned to CT-P17 at Day 1 (Week 0) continued their treatment with CT-P17. Patients who were randomized to CT-P17 or EU-approved Humira received assigned study drug EOW from Week 26 and thereafter up to Week 48. Only the study center visits are presented in this figure.

[1] An EOS visit occurred at Week 52 for all patients who completed or discontinued the study treatment. The patients who discontinued early from the study treatment also visited the study center until Week 52 by regular scheduled time interval for efficacy and safety assessments, even if they initiated RA medication changes (including those prohibited by the protocol).

[2] An independent joint count assessor assigned to each study center assessed joint counts. If possible, it was recommended that the joint count assessments were performed independently by the same person at each study center throughout the entire study period.

[3] Usability assessments were performed only for patients who self-injected the study drug (Bulgaria and Poland only). For patients who the caregiver or trained study center staff injected the study drug, usability assessment was unnecessary.

Source: Applicant s ctp1731-body, page 40, Figure 9-1

Approximately 564 male and female patients with moderate to severe active RA were planned to be enrolled in a 1:1 ratio into the CT-P17 or EU-approved Humira treatment groups. The duration of the study was 58-weeks, which included Screening (up to 6 weeks) and the last dose at 48 weeks plus the following 4 weeks off-dose period, prior to the End-of-Study (EOS) visit.

The Screening Period took place between Days -42 and Day -1 prior to the first study drug administration.

The Treatment Period comprised two periods as follows:

- Treatment Period I (from Week 0 to Week 24)
- Treatment Period II (after Treatment Period I and prior to EOS visit, from Week 26 to Week 48)

On Day 1, subjects who met all the inclusion criteria and none of the exclusion criteria were enrolled in the study and randomly assigned to receive either CT-P17 or EU-Humira prior to treatment using a 1:1 allocation ratio. Prior to dosing at Week 26, all subjects underwent the second randomization process. Subjects who were initially randomly assigned to EU-approved Humira were randomized again in a ratio of 1:1 to either continue EU-approved Humira or undergo a single transition to CT-P17. All subjects who were initially randomly assigned to CT-P17 at Day 1 continued their treatment with CT-P17. Subjects who were randomized to CT-P17 or EU-approved Humira received the assigned study drug EOW from Week 26 and thereafter up to Week 48.

The subjects received either CT-P17 40 mg or EU-Humira 40 mg, as per first and second randomization, by SC injection EOW, co-administered with MTX between 12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or parenteral dose (intramuscular or SC; dose and route were maintained from beginning to EOS), and folic acid (≥5 mg/week, oral dose).

All subjects returned to the study center at regularly scheduled time intervals for clinical assessments and blood samplings. At each visit, the subject was questioned about AEs and concomitant medications and was monitored for the clinical signs and symptoms of tuberculosis (TB). Table 12 show the schedule of events.

Table 12. Schedule of Events

	Screening	Treatment Period I									Treatment Period II							EOS [1]
		Dose 1	Dose 2	Dose 3	Dose 4[3]	Dose 5	Dose 7	Dose 9	Dose 11	Dose 13	Dose 14	Dose 15	Dose 17	Dose 19	Dose 21	Dose 23	Dose 25	
Study visit[2] (Week)	-6	0	2	4	6[3]	8	12	16	20	24	26	28	32	36	40	44	48	52
Study visit[2] (Day)	-42 to -1	1	15	29	43[3]	57	85	113	141	169	183	197	225	253	281	309	337	365
Informed consent	X																	
Demographics, height, medical history	X																	
Hepatitis-B/C and HIV-test[4]	X										(X)							(X)
Serum pregnancy test[5]	X																	X
Chest X-ray[6]	X																	X
IGRA[7]	X						X[8]			X[8]								X
Inclusion/ exclusion criteria	X	X[8]																
Randomization		X[9]									X[9]							
Efficacy assessments[8,10] – Pre-dose																		
Swollen joint count (66 joints/ 28 joints)	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Tender joint count (68 joints/ 28 joints)	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
VAS pain score	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
VAS global assessment of disease activity (patient/physician) scores	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Health assessment questionnaire	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
CRP[11]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
ESR (local)[11]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
QoL (SF-36) assessment	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Hand and foot X-ray[12]	X																	X
Safety and other assessments[8] – Pre-dose																		
Physical examination, vital signs, and weight	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[13]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[5]		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[14]	X	X								X								X
Immunogenicity[15]		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Treatment Period I									Treatment Period II							EOS [1]
		Dose 1	Dose 2	Dose 3	Dose 4[3]	Dose 5	Dose 7	Dose 9	Dose 11	Dose 13	Dose 14	Dose 15	Dose 17	Dose 19	Dose 21	Dose 23	Dose 25	
Study visit[2] (Week)	-6	0	2	4	6[3]	8	12	16	20	24	26	28	32	36	40	44	48	52
Study visit[2] (Day)	-42 to -1	1	15	29	43[3]	57	85	113	141	169	183	197	225	253	281	309	337	365
Pharmacokinetic blood sampling[16]		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Rheumatoid factor		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-CCP		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Biomarker[17]		X																
Study treatment[18,19]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PRE- and POST-SIAQ[20]				X	X	X				X								
Self-injection assessment checklist by observer[21]				X	X	X				X								
Hypersensitivity/ allergic reactions monitoring[22] and injection site reaction[23]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Local site pain by VAS[24]		X	X	X		X		X		X	X		X	X		X	X	
Prior, concomitant medications[25]	X																	
TB clinical monitoring[26]	X																	
AEs[27]	X																	

Abbreviations: AE, adverse event(s); anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; ECG, electrocardiogram; eCRF, electronic case report forms; EOS, end-of-study; EOW, every other week; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; IGRA, interferon-γ release assay; ICF, informed consent form; IM, intramuscular; QoL, quality of life; SC, subcutaneous; SIAQ, self-injection assessment questionnaire; TB, tuberculosis; VAS, visual analogue scale.

* Note: Only the study center visits are presented in this table. As the study drug was administered EOW, the planned injections on Weeks 10, 14, 18, 22, 30, 34, 38, 42, and 46, which were not specified in this table could be self-administered or by the caregiver at home. The patients who discontinued early from the study treatment also visited the study center until Week 52 by regular scheduled time interval for efficacy and safety assessments, even if they initiated rheumatoid arthritis (RA) medication changes (including those prohibited by the protocol). However, any assessment(s) that could jeopardize the patients' safety could be skipped, as per investigator judgement.

The End-of-Study visit occurred at Week 52 for all subjects who completed or discontinued the study treatment. The subjects who discontinued early from the study treatment visited the study center until Week 52 by regular scheduled time interval for efficacy and safety assessments, even if they initiated RA medication changes (including those prohibited by the protocol).

The primary endpoint proposed for Study CT-P17 3.1 was the proportion of subjects achieving a clinical response according to the ACR20 at Week 24. The ACR definition of 20% improvement criteria is the current gold-standard for assessment of RA efficacy. An ACR20 is achieved when the following criteria are met: at least 20% improvement in tender and swollen joint counts, and at least 20% improvement in three of the five remaining ACR core set measures (subject's and physician's global assessments, pain, disability, and an acute phase reactant).

The ACR20 is a validated composite measure of efficacy which corresponds closely to clinicians' impression of subject improvement and discriminates powerfully between active and placebo treatment and classifies a subject as a responder or nonresponder based on multiple ACR criteria. Using a composite endpoint as primary outcome is preferable, compared to the use of multiple single endpoints, as the latter increases the likelihood of detecting a difference between therapies when no real difference exists (type I error) and makes it difficult to interpret the difference between therapies when only some of the outcomes are statistically significant. Using a validated composite endpoint resolves these issues, and ACR20 response has been extensively used as a primary endpoint in RA trials evaluating the efficacy of anti-rheumatic drugs, including US-Humira.

Consequently, in selecting the primary endpoint for this study, the validity and broad use of ACR20 has been taken into account, as well as the proven ability for ACR20 to detect differences in clinical response between EU-Humira and placebo.

The proposed safety monitoring was deemed to be sufficient to monitor potential risks of CT-P17 administration. In view of the structural, biological, and toxicological similarity to EU-Humira, CT-P17 was expected to display a similar safety profile. Therefore, safety monitoring was based on the safety profile for EU-Humira.

The study was unblinded for reporting after completion of Week 24 of all subjects and efficacy, PK, PD, usability, immunogenicity, and safety endpoints were evaluated by predefined unblinded Applicant teams. The investigators, subjects, and Applicant teams remained blind until the end of the study. After study completion of all subjects, the additional code breaking for Treatment Period II had been performed for statistical analysis and medical writing for this final CSR.

Major inclusion criteria included the following:

- Male or female between 18 to 75 years-old
- Subject had a diagnosis of RA according to the 2010 ACR/EULAR classification criteria for at least 24 weeks prior to the first administration of the study drug
- Subject had active disease as defined by the presence of 6 or more swollen joints (of 66 assessed), 6 or more tender joints (of 68 assessed), and either an erythrocyte sedimentation rate (ESR) >28 mm/hour or a serum C-reactive protein (CRP) concentration >1.0 mg/dL (>10 mg/L) at Screening.

- Subject had been receiving oral or parenteral MTX at a dose of between 12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, for at least 12 weeks and had been on a stable dose and route of MTX for at least 4 weeks prior to the first administration of the study drug.
- Subject had adequate renal and hepatic function at Screening.
- Subject had adequate hematology laboratory test results at Screening.
- Subject and their partner of childbearing potential had to agree to use a highly effective method of contraception throughout the study and for 6 months after the last dose of assigned treatment. Examples include the following:
    - Hormonal contraceptives (combined or progestogen-only) associated with inhibition of ovulation
    - Intrauterine devices
    - Sexual abstinence
- Subject had to be able and willing to self-administer SC injections or designate a qualified person(s) to administer SC injection.

Major exclusion criteria included the following:

- Subject had previously received investigational or licensed product; biologic or targeted synthetic DMARDs (e.g., tofacitinib, baricitinib) for the treatment of RA and/or TNFα inhibitor for any purposes.
- Subject currently had or had a history of any of the following infections:
    - A known infection with hepatitis B (active or carrier of hepatitis B), hepatitis C, or infection with human immunodeficiency virus (HIV). However, a subject with past hepatitis B virus was allowed if resolved.
    - Acute infection requiring oral antibiotics within 2 weeks or parenteral injection of antibiotics within 4 weeks prior to the first administration of the study drug.
    - Recurrent herpes zoster or other chronic or recurrent infection within 6 weeks prior to the first administration of the study drug.
    - Past or current granulomatous infections or other severe or chronic infections (such as sepsis, abscess, opportunistic infections, or invasive fungal infections such as histoplasmosis). A subject who had a past diagnosis with sufficient documentation of complete resolution of the infection could be enrolled in the study.
    - Other serious infections within 24 weeks prior to the first administration of the study drug.
    - Subject currently had or had a history of any of TB.
- Subject had a medical condition including one or more of the following:
    - Classified as Class II or III obese by world health organization classification
    - Uncontrolled diabetes mellitus, even after insulin treatment
    - Uncontrolled hypertension (as defined by systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥100 mmHg)
    - Any other inflammatory or rheumatic diseases, including but not limited to psoriatic arthritis, AS, spondyloarthritis, systemic lupus erythematosus,

Lyme disease or fibromyalgia, that may confound the evaluation of the effect of the study drug
    - Significant systemic RA involvement (e.g., Sjögren's syndrome, vasculitis, pulmonary fibrosis) which would put the subject at risk if they were enrolled.
    - A known malignancy within the previous 5 years prior to the first administration of the study drug except completely excised and cured squamous carcinoma of the uterine cervix in situ, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma.
    - New York Heart Association (NYHA) Class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina or clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction within 24 weeks prior to the first administration of the study drug.
    - History of organ transplantation, including corneal graft/transplantation.
    - Any clinically significant respiratory disease, including but not limited to chronic obstructive pulmonary disease, asthma or pleural effusion.
    - Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain-Barre syndrome.
    - Any conditions significantly affecting the nervous system (e.g., neuropathic conditions or nervous system damage) if it could interfere with the investigator's assessment on disease activity scores including joint counts.
    - Any other serious acute or chronic medical or psychiatric condition that could increase the risk associated with study participation or study drug administration or that could interfere with the interpretation of study results.
- Subject had received or planned to receive any of the following prohibited medications or treatment:
    - Intra-articular corticosteroids within 4 weeks prior to the first administration of the study drug . Subjects were permitted to receive either oral or parenteral glucocorticoids (≤10 mg daily of prednisone/prednisolone or equivalent), and NSAID, if they had received a stable dose for at least 4 weeks prior to the first administration of the study drug and the same dose had to be maintained until the primary endpoint assessment at Week 24. In addition, subjects were permitted to receive low-potency topical, otic, and ophthalmic glucocorticoid preparations provided the preparations were administered per the instructions on the product label.
    - Conventional DMARDs, other than MTX, including hydroxychloroquine, chloroquine, or sulfasalazine, within 4 weeks prior to the first administration of the study drug . Subjects who had discontinued leflunomide and had successful chelation with 8 g of cholestyramine (3 times daily) for 11 days had to wait 4 weeks after the last dose of cholestyramine prior to the first administration of the study drug . Subjects who discontinued leflunomide and did not have a cholestyramine washout had to wait 12 weeks after the last dose of leflunomide prior to the first administration of the study drug.

  - Alkylating agents within 1 year prior to the first administration of the study drug.
  - Herbal products within 2 weeks prior to the first administration of the study drug
  - Live or live-attenuated vaccine within 4 weeks prior to the first administration of the study drug , or any planned live or live-attenuated vaccination during the study period.
  - Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement) within 12 weeks prior to the first administration of the study drug or planned within 24 weeks after the first administration of the study drug.
- Female subjects who were pregnant or breastfeeding or planned to become pregnant or breastfeed within 6 months of the last dose of study drug.

Overall, Study CT-P17 3.1 was adequately designed and sufficiently conducted to allow for adequate exposure to CT-P17 and EU-Humira to detect any potential differences.

Statistical Methodologies

This Statistical Analysis Plan (SAP) – Version 2.0, issued on 19th June 2020, defined the statistical methods to be used by CELLTRION Clinical Statistics team in the analysis and presentation of data from CELLTRION study number CT-P17 3.1.

Analysis populations were used for the summary of the Treatment Period I (Week 0 to Week 24 visit and before study drug administration of Week 26 visit). Analysis subsets were used only for the summary of the Treatment Period II (Baseline, Week 26 to Week 48 visit and EOS visit). The following analysis sets were defined:

- *The Intent-to-Treat (ITT) population* was defined as all patients enrolled and randomly assigned to receive a dose of either of the study drugs, regardless of whether or not any study drug dosing was completed. All efficacy evaluations were based on the ITT population.
- *Per-protocol (PP) population* was defined as all randomly assigned patients who have received all full doses of study drug up to Week 22 (total of 12 injections) and have an ACR assessment at Week 24. A major protocol deviation that may affect the interpretation of study results of primary efficacy endpoint was excluded from PP population. Final determinations of the PP population were made at the blinded data review meeting (DRM).
- *The ITT population – Treatment Period II subset* was defined as all patients in ITT population who are randomly assigned to receive a dose of either of the study drugs prior to dosing at Week 26, regardless of whether or not any study drug dosing was completed.
- *PP population – Treatment Period II subset* consisted of all patients in PP population who receive at least 1 dose (full) of either of the study drugs on or after Week 26 and have at least 1 post treatment efficacy assessment after first study drug administration in Treatment Period II.

- *Safety population* consisted of all patients who receive at least 1 dose (full or partial) of either of the study drugs. The safety population will be the primary population for the summary of safety data.

The following demographic measures and stratification details were summarized for the ITT population and for the ITT population – Treatment Period II subset by treatment group: Age (years); Gender (male, female); Female Fertility Status (pre-menarche, surgically sterilized, post-menopausal, potentially able to bear children, other); Race (Asian, White, Black or African American, not allowed by investigator country regulations, other); Ethnicity (Hispanic or Latino, non-Hispanic or non-Latino, unknown); Height (cm), Weight (kg) and Body Mass Index (BMI) (kg/m2) as recorded at Screening; Country; SDAI at Screening (high (SDAI>26) vs. not high (SDAI≤26)) and SDAI at Week 24 (remission (SDAI≤3.3) vs. non-remission (SDAI>3.3)). The number and percentage of SDAI at Week 24 were to be presented in the summary of Treatment Period II. The stratification factors were to be summarized using the final data collected on eCRF. Demographics and stratification details were planned to be presented in separate listings for the ITT population by treatment group.

A sample size of 450 patients (225 patients in each treatment group of CT-P17 and EU-approved Humira) lead to 80% statistical power for the demonstration of similarity of ACR20 at Week 24 based on the expected ACR20 rate of 63% with an similarity margin of (–12% to 15%) using a two one-sided 5% significance level of an similarity test. The drop-out rate had been hypothesized at 20%; therefore, approximately 564 patients (282 patients in each treatment group of CT-P17 and Humira) were planned to be randomized.

Based on the review of the previous BPD Type 2 Meeting briefing document (submitted on March 30th, 2018), to justify the lower bound of -12%, the applicant performed a meta-analysis of four historical studies and results are given below (**Table 13**). The applicant justified the upper bound of +15% by citing the precedence of similar margins used in FDA approval of anti-TNF biosimilars. Moreover, the applicant claimed that the toxicity of adalimumab is known to be dose independent, which could provide a satisfactory justification for choosing an asymmetrical margin.

Table 13. Historical Effect of Adalimumab on ACR20 Response in Randomized Clinical Trials of Patients with Active RA Despite Treatment with Methotrexate (MTX)

Study	Week	MTX + Placebo N	MTX + Placebo ACR Response	MTX + Adalimumab N	MTX + Adalimumab ACR Response	Difference in % Response
Keystone[1]	24	200	30%	207	63%	34%
Weinblatt[2]	24	62	15%	67	67%	53%
Kim[3]	24	63	37%	65	62%	25%
Chen[4]	12	12	33%	35	54%	21%
Meta-Analysis (fixed effects[5]): Difference (95% CI)						35.0% (28.2%,41.9%)
Meta-Analysis (random effects[6]): Difference (95% CI)						35.4% (22.5%, 48.2%)
Heterogeneity p-value						0.04

Source: Statistical Reviewer

[1] Keystone, E. C., Kavanaugh, A. F., Sharp, J. T., Tannenbaum, H., Hua, Y., Teoh, L. S., ... & Chartash, E. K. (2004). Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti–tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: A randomized, placebo-controlled, 52-week trial. Arthritis & Rheumatism, 50(5), 1400-1411.

[2] Weinblatt, M. E., Keystone, E. C., Furst, D. E., Moreland, L. W., Weisman, M. H., Birbara, C. A., ... & Chartash, E. K. (2003). Adalimumab, a fully human anti–tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis & Rheumatism, 48(1), 35-45.

[3] KIM, H. Y., LEE, S. K., SONG, Y. W., YOO, D. H., KOH, E. M., Yoo, B., & Luo, A. (2007). A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR Journal of Rheumatology, 10(1), 9-16.

[4] Chen, D. Y., Chou, S. J., Hsieh, T. Y., Chen, Y. H., Chen, H. H., Hsieh, C. W., & Lan, J. L. (2009). Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. Journal of the Formosan Medical Association, 108(4), 310-319

[5] Based on Mantel-Haenszel weights

[6] Based on DerSimonian-Laird weights

The proportion of patients achieving clinical response (responder/non-responder) according to ACR20 criteria at Week 24 was analyzed as a primary endpoint. The American College of Rheumatology (ACR) criteria are standard measures of clinical activity in RA patients. The ACR criteria used in this study are ACR20, ACR50 and ACR70. A patient was defined as a responder according to ACR20 criteria if the followings were fulfilled:

- A decrease of at least 20% in the number of tender joints (based on 68 joints)
- A decrease of at least 20% in the number of swollen joints (based on 66 joints), and
- A 20% improvement in at least 3 of the following:
    - Patient's assessment of pain (VAS scale, mm)
    - Patient's global assessment of disease activity (VAS scale, mm)
    - Physician's global assessment of disease activity (VAS scale, mm)

- HAQ estimate of physical ability
- Serum CRP (mg/dL) concentration or ESR (mm/h)

The following categories of patients were considered non-responders:

- Patients with an improvement according to the ACR criteria of less than 20%
- Patients who terminated from the study prior to the week of interest
- Patients who continued the study/study treatment but did not visit the site for the evaluation of ACR20 at the week of interest
- Patients with incomplete data for evaluation of ACR20 criteria at the week of interest; if ACR20 criteria could be fulfilled with non-missing component, regardless of missing component, the patient is considered as responder.

Primary estimand was not defined in the SAP, however, study treatment discontinuation before Week 24 was planned to be handled with a treatment policy strategy, using all observed data regardless of study treatment adherence.

The primary analysis was conducted by the exact binomial approach using a Farrington-Manning score method (Chan and Zhang, 1999; Inverting two one-sided test), and the 90% CI for the difference in proportion between the 2 treatment groups was produced. Therapeutic similarity of clinical response according to ACR20 criteria was concluded if the 90% CIs for the treatment difference are entirely within the limits of -12% to 15% at Week 24. The primary efficacy analysis was conducted on both the ITT and the PP population.

In order to evaluate the treatment effect based on the patients who are remaining in the study and continuing study treatment through Week 22, the primary analysis was repeated for ITT population, regarding the patients who skipped at least 1 study drug administration, or discontinued from the study treatment before Week 24 as non-responders. In addition, in order to evaluate impact of missing data, tipping point analysis was conducted for the primary efficacy endpoint for ITT population, under various missing data assumptions to explore the sensitivity of results to violations in assumptions about the missing data. For the missing data (patients who terminated the study before Week 24, who continued the study/study treatment but did not visit the site for the evaluation of ACR20 at Week 24, or with incomplete data for evaluation of ACR20 criteria at Week 24), imputed values as responder were shifted gradually by treatment groups to make various missing data assumptions. The 90% CI of the difference of ACR20 response proportion at Week 24 between the two treatment groups (CT-P17 and EU-Humira) was calculated using the Farrington-Manning score method, and scenarios were to be displayed through a shift table.

As the exact binomial approach does not allow for stratification, a sensitivity analysis was performed on the primary efficacy endpoint, using the logistic regression model with treatment group as a fixed effect and country and disease activity by SDAI at Screening as covariates. If country was found to be unsuitable as a covariate due to the number of levels, then this was pooled into a new variable, region was to be used instead. Categorization of the region was discussed in DRM.

For evaluating the treatment effect of each of the ACR components, treatment differences at Week 24 between the 2 treatment groups and 95% CIs of the treatment difference for each of the ACR components were presented on the ITT population. The secondary efficacy endpoints were as below.

- ACR criteria (individual components, ACR20 except for Week 24, ACR50 and ACR70)
- Hybrid ACR response
- DAS28 (individual components, DAS28[ESR] and DAS28[CRP])
- European League Against Rheumatism (EULAR) response criteria
- Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI)
- Short-Form Health Survey (SF-36)
- Joint Damage Progression

Subject Disposition

Overall, approximately 94% of the randomized patients completed treatment period I. The study treatment discontinuation rates were numerically similar across treatment groups (21 [6.5%] patients in the CT-P17 treatment group and 19 [5.9%] patients in the EU-approved Humira treatment group). The most frequently reported reason for discontinuing study treatment was withdrawal by patient followed by AE. Of the 40 (6.2%) patients who discontinued the study treatment, 32 (4.9%) patients terminated the study and 8 patients remained in the study for safety and efficacy follow-up. The proportion of patients who terminated the study was numerically similar between the two treatment groups (17 [5.2%] patients in the CT-P17 treatment arm and 15 [4.6%] patients in the EU-approved Humira treatment group). The most frequently reported reason for discontinuing study treatment was withdrawal by patient. The reasons for discontinuation from treatment or discontinuation from study for both treatment groups were numerically similar.

Table 14: Disposition of Patients (Treatment Period I) in Study CT-P17 3.1 - ITT population

Treatment Period I Status	CT-P17 (N=324)	EU-Humira (N=324)	Total (N=648)
Completed	**303 (93.5%)**	**305 (94.1%)**	**608 (93.8%)**
Reasons for Discontinuing Study Treatment	**21 (6.5%)**	**19 (5.9%)**	**40 (6.2%)**
Adverse Event	7 (2.2%)	8 (2.5%)	15 (0.3%)
Significant Protocol Deviation	1 (0.3%)	1 (0.3%)	2 (0.3%)
Lost To Follow-Up	2 (0.6%)	0	2 (0.3%)
Investigator Decision	1 (0.3%)	0	1 (0.2%)

Withdrawal by Patient	9 (2.8%)	8 (2.5%)	17 (2.6%)
Others	1 (0.3%)	2 (0.6%)	3 (0.5%)
Reasons for Terminating Study	**17 (5.2%)**	**15 (4.6%)**	**32 (4.9%)**
Withdrawal by Patient	15 (4.6%)	14 (4.3%)	29 (4.5%)
Lost To Follow-Up	2 (0.6%)	0	2 (0.3%)
Others	0	1 (0.3%)	1 (0.2%)

Source: Statistical Reviewer
Note: Among the 32 terminated patients, 5 of them provided the ACR20 scores at Week 24, leading to 27 patients with missing data for the primary endpoint.

Demographics and Baseline Characteristics

Patient demographics and stratification details were generally comparable between the two treatment groups (Table 15). Patients were on average 52 years of age, more frequently female (79%), more frequently white (92%), and neither Hispanic nor Latino (90%). The randomized patients were mainly from Eastern Europe and the majority of patients were from Poland (71%). The majority of patients had high disease activity based on SDAI score (SDAI >26) at Screening (90%).

Table 15: Demographics and Stratification Details in Study CT-P17 3.1 - ITT population

	CT-P17 (N=324)	EU-Humira (N=324)	Total (N=648)
Age (years), Mean (SD)	52.0 (12.1)	51.8 (11.8)	51.9 (12.0)
Female, n (%)	249 (76.9)	265 (81.8)	514 (79.3)
Female Fertility Status, n (%)			
Surgically sterilized	16 (6.4)	14 (5.3)	30 (5.8)
Post-menopausal	129 (51.8)	147 (55.5)	276 (53.7)
Potentially able to bear children	104 (41.8)	104 (39.2)	208 (40.5)
Race, n (%)			
White	299 (92.3)	298 (92.0)	597 (92.1)
Other	25 (7.7)	26 (8.0)	51 (7.9)
Ethnicity, n (%)			
Hispanic or Latino	29 (9.0)	34 (10.5)	63 (9.7)
Non-Hispanic or Non-Latino	295 (91.0)	290 (89.5)	585 (90.3)
Screening Height (cm), Mean (SD)	165.1 (9.2)	165.4 (8.7)	165.3 (9.0)
Screening Weight (kg), Mean (SD)	72.6 (14.3)	73.2 (14.2)	72.9 (14.2)
Screening BMI (kg/m^2), Mean (SD)	26.6 (4.2)	26.7 (4.3)	26.6 (4.2)

Country, n (%)			
Bulgaria	20 (6.2)	19 (5.9)	39 (6.0)
Hungary	17 (5.2)	17 (5.2)	34 (5.2)
Lithuania	4 (1.2)	5 (1.5)	9 (1.4)
Peru	25 (7.7)	26 (8.0)	51 (7.9)
Poland	231 (71.3)	231 (71.3)	462 (71.3)
Ukraine	27 (8.3)	26 (8.0)	53 (8.2)
SDAI at Screening, n (%)			
SDAI≤26	30 (9.3)	34 (10.5)	64 (9.9)
SDAI>26	294 (90.7)	290 (89.5)	584 (90.1)

Source: Statistical Reviewer
Abbreviations: BMI, body mass index; ITT, intent-to-treat; SD, standard deviation; SDAI, simplified disease activity index.
Note: Height, weight and BMI results summarized were the screening assessment values.

Analysis of Primary Clinical Endpoint(s)

Table 16 displays results form the primary efficacy analysis in Study CT-P17. Approximately 82.7% of patients randomized to CT-P17 and 82.7% of patients randomized to EU-Humira achieved an ACR20 response (responder) at Week 24, for an estimated proportion difference of 0 (90% CI: -4.98, 4.98). The 90% CI ruled out the similarity margin of (-12%, 15%) proposed by the applicant, which demonstrated therapeutic similarity between the two treatment groups. In a supportive analysis of ACR20 response in the subset of patients who completed the study and adhered to the protocol (PP population), 87.0% and 86.9% responded on CT-P17 and EU-Humira, respectively, for an estimated difference of 0.06% (90% CI: -4.70%, 4.86%) meeting the similarity margin of (-12% to 15%) (Table 16).

Table 16: Difference (90% CI) in the Proportion of ACR20 at Week 24 by Treatment Group in Study CT-P17 3.1 - Primary Efficacy Analysis

Population	**ACR20 Response Rate**		**Treatment Difference Estimate (%) 90% CI of Treatment Difference (%)[1]**
	CT-P17 (N = 324)	**EU-Humira (N = 324)**	**CT-P17 vs EU-Humira**
ITT Population	268/324 (82.7%)	268/324 (82.7%)	0.00 (-4.98, 4.98)
PP Population	240/276 (86.9%)	240/276 (86.9%)	0.06 (-4.70, 4.86)

Source: Statistical Reviewer
[1] The exact binomial approach using a Farrington-Manning score method was used to evaluate the 90% confidence interval for the difference in proportion between the two treatment groups. Patients who terminated the study prior to the week of interest, who continued the study/study treatment but did not visit the site for the evaluation of ACR20 at the week of interest, and with incomplete data for evaluation of ACR20 criteria at the week of interest were considered as nonresponder. The ITT population was the primary population for the primary endpoint.

Additional supportive analysis based on the logistic regression model with treatment group as a fixed effect and country and disease activity by SDAI at Screening as covariates was consistent with the above findings (**Table 17**).

Table 17: Difference (90% CI) in the Proportion of ACR20 at Week 24 by Treatment Group in Study CT-P17 3.1 - Supportive Analysis

ITT Population	ACR20 Response Rate		Treatment Difference Estimate (%) 90% CI of Treatment Difference (%)
	CT-P17 (N = 324)	EU-Humira (N = 324)	CT-P17 vs EU-Humira
Logistic Regression[1]	268/324 (82.7%)	268/324 (82.7%)	0.06 (-4.81, 4.93)

Source: Statistical Reviewer
[1] Estimates of the 90% confidence interval were estimated from the logistic regression results using the Delta method.

Potential Effects of Missing Data

There were 27 patients who terminated the study before Week 24 and were missing in data (15 [4.6%] patients in the CT-P17 treatment group and 12 [3.7%] patients in the EU-approved Humira treatment group). The applicant included tipping point analysis to explore the sensitivity of results to violations in assumptions about the missing data in the primary efficacy analysis. By exploring all possible missing data assumptions, (i.e., imputing different number of responders for 15 patients from the CT-P17 treatment group and 12 patients from the EU-Humira treatment group who have missing ACR20 data), the resulting 90% confidence intervals were included in the similarity margin of (-12%, 15%), which were consistent with the primary analysis result (**Figure 13**). Therefore, the tipping point results were supportive of the finding of no meaningful differences in efficacy or loss of efficacy between products.

Figure 13: Tipping Point Results for the Proportion of Patients Achieving Response According to ACR20 at Week 24 in Study CT-P17 3.1 (ITT Population)

		Shift for the Number of Responders in EU-Humira®[1]												
		0	1	2	3	4	5	6	7	8	9	10	11	12
Shift for the Number of Responders in CT-P17[1]	0	-4.89, 4.89	-5.18, 4.56	-5.47, 4.23	-5.76, 3.91	-6.05, 3.58	-6.34, 3.26	-6.63, 2.93	-6.92, 2.60	-7.21, 2.27	-7.50, 1.95	-7.79, 1.62	-8.08, 1.29	-8.37, 0.96
	1	-4.56, 5.18	-4.85, 4.85	-5.14, 4.53	-5.43, 4.20	-5.72, 3.87	-6.01, 3.55	-6.31, 3.22	-6.60, 2.89	-6.89, 2.56	- 7.18, 2.24	-7.47, 1.91	-7.76, 1.58	-8.04, 1.25
	2	-4.23, 5.47	-4.53, 5.14	-4.82, 4.82	-5.11, 4.49	-5.40, 4.16	-5.69, 3.84	-5.98, 3.51	-6.27, 3.18	-6.56, 2.85	-6.85, 2.53	-7.14, 2.20	-7.43, 1.87	-7.72, 1.54
	3	-3.91, 5.76	-4.20, 5.43	-4.49, 5.11	-4.78, 4.78	-5.07, 4.45	-5.36, 4.13	-5.65, 3.80	-5.94, 3.47	-6.23, 3.14	-6.52, 2.82	-6.81, 2.49	-7.10, 2.16	-7.39, 1.83
	4	-3.58, 6.05	-3.87, 5.72	-4.16, 5.40	-4.45, 5.07	-4.74, 4.74	-5.03, 4.42	-5.32, 4.09	-5.61, 3.76	-5.90, 3.43	-6.19, 3.11	-6.48, 2.78	-6.77, 2.45	-7.06, 2.12
	5	-3.26, 6.34	-3.55, 6.01	-3.84, 5.69	-4.13, 5.36	-4.42, 5.03	-4.71, 4.71	-5.00, 4.38	-5.29, 4.05	-5.58, 3.72	-5.86, 3.40	-6.15, 3.07	-6.44, 2.74	-6.73, 2.41
	6	-2.93, 6.63	-3.22, 6.31	-3.51, 5.98	-3.80, 5.65	-4.09, 5.32	-4.38, 5.00	-4.67, 4.67	-4.96, 4.34	-5.25, 4.01	-5.54, 3.68	-5.83, 3.36	-6.11, 3.03	-6.40, 2.70
	7	-2.60, 6.92	-2.89, 6.60	-3.18, 6.27	-3.47, 5.94	-3.76, 5.61	-4.05, 5.29	-4.34, 4.96	-4.63, 4.63	-4.92, 4.30	-5.21, 3.97	-5.50, 3.65	-5.79, 3.32	-6.07, 2.99
	8	-2.27, 7.21	-2.56, 6.89	-2.85, 6.56	-3.14, 6.23	-3.43, 5.90	-3.72, 5.58	-4.01, 5.25	-4.30, 4.92	-4.59, 4.59	-4.88, 4.26	-5.17, 3.93	-5.46, 3.60	-5.75, 3.28
	9	-1.95, 7.50	-2.24, 7.18	-2.53, 6.85	-2.82, 6.52	-3.11, 6.19	-3.40, 5.86	-3.68, 5.54	-3.97, 5.21	-4.26, 4.88	-4.55, 4.55	-4.84, 4.22	-5.13, 3.89	-5.42, 3.56
	10	-1.62, 7.79	-1.91, 7.47	-2.20, 7.14	-2.49, 6.81	-2.78, 6.48	-3.07, 6.15	-3.36, 5.83	-3.65, 5.50	-3.93, 5.17	-4.22, 4.84	-4.51, 4.51	-4.80, 4.18	-5.09, 3.85
	11	-1.29, 8.08	-1.58, 7.76	-1.87, 7.43	-2.16, 7.10	-2.45, 6.77	-2.74, 6.44	-3.03, 6.11	-3.32, 5.79	-3.60, 5.46	-3.89, 5.13	-4.18, 4.80	-4.47, 4.47	-4.76, 4.14
	12	-0.96, 8.37	-1.25, 8.04	-1.54, 7.72	-1.83, 7.39	-2.12, 7.06	-2.41, 6.73	-2.70, 6.40	-2.99, 6.07	-3.28, 5.75	-3.56, 5.42	-3.85, 5.09	-4.14, 4.76	-4.43, 4.43
	13	-0.64, 8.66	-0.93, 8.33	-1.22, 8.01	-1.50, 7.68	-1.79, 7.35	-2.08, 7.02	-2.37, 6.69	-2.66, 6.36	-2.95, 6.03	-3.23, 5.70	-3.52, 5.37	-3.81, 5.04	-4.10, 4.71
	14	-0.31, 8.95	-0.60, 8.62	-0.89, 8.29	-1.18, 7.97	-1.46, 7.64	-1.75, 7.31	-2.04, 6.98	-2.33, 6.65	-2.62, 6.32	-2.91, 5.99	-3.19, 5.66	-3.48, 5.33	-3.77, 5.00
	15	0.02, 9.24	-0.27, 8.91	-0.56, 8.58	-0.85, 8.25	-1.14, 7.93	-1.42, 7.60	-1.71, 7.27	-2.00, 6.94	-2.29, 6.61	-2.58, 6.28	-2.86, 5.95	-3.15, 5.62	-3.44, 5.29

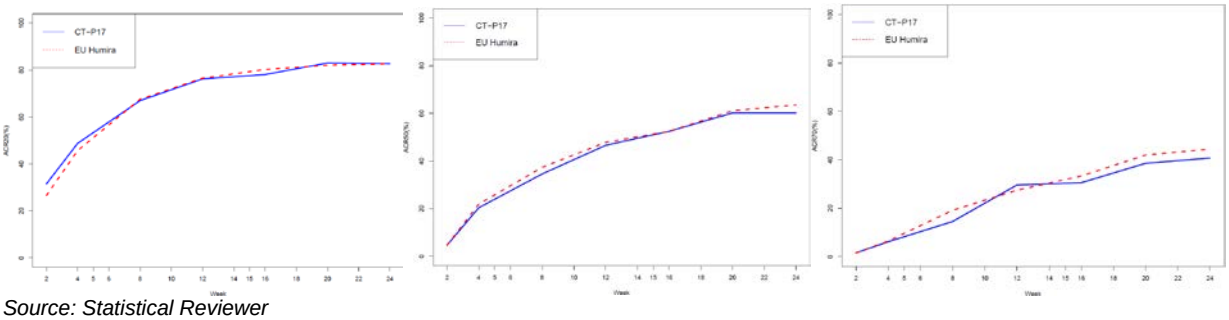
Source: Applicant's summary of clinical efficacy, Page 26, Table 2.7.3-10

[1] 15 (4.63%) patients in the CT-P17 treatment group and 12 (3.70%) patients in the EU-Humira® treatment group were reported to be terminated from the study before Week 24 and missing in data. For the missing data (patients who were terminated from the study before Week 24, who continued the study/study treatment but did not visit the site for the evaluation of ACR20 at Week 24, or with incomplete data for evaluation of ACR20 criteria at Week 24), imputed values as responder were shifted gradually by treatment groups to make MNAR (Missing Not at Random) scenarios. The 90% CI of the difference of ACR20 response proportion at Week 24 between the two treatment groups (CT-P17 and EU-Humira®) was calculated using asymptotic method using a Farrington-Manning score method.

Analysis of Secondary Clinical Endpoint(s)

The proportions of patients remaining in the study and achieving ACR20 responses at Weeks 2, 4, 8, 12, 16, 20 and 24, in addition to ACR50 and ACR70 response probabilities over time, were similar between the treatment groups (**Figure 14**). Mean changes from baseline in the components of the ACR composite endpoint and the disease activity score (DAS28-CRP and DAS28-ESR) were also similar between the groups in all randomized patients who completed the study (**Table 18**).

Figure 14: ACR20/50/70 Response[1] Probabilities over Time in Study CT-P17 3.1 (ITT Population)



Source: Statistical Reviewer
[1] Defined by remaining in the study and meeting ACR20 response criteria at Weeks 2, 4, 8, 12, 16, 20 and 24

Table 18: Mean Changes from Baseline and Treatment Difference for ACR Components and DAS28 Score at Week 24 in Study CT-P17 3.1 (ITT Population)

Parameter	CT-P17 (N=324)		EU-Humira (N=324)		Difference (95% CI)[2]
	N[1]	Mean	N[1]	Mean	
Tender Joint Count of 68 Joints	309	-15.6	312	-15.0	-0.7 (-2.2, 0.7)
Swollen Joint Count of 68 Joints	309	-11.7	312	-11.6	-0.2 (-1.1, 0.8)
Patient's Assessment of Pain	309	-43.5	312	-46.0	2.4 (-1.8, 6.5)
Patient's Global Assessment of Disease Activity	309	-43.4	312	-45.3	1.6 (-2.5, 5.7)
Physician's Global Assessment of Disease Activity	309	-48.1	312	-49.0	0.6 (-2.5, 3.6)
HQA Estimate of Physical Ability	309	-0.6	312	-0.6	0.04 (-0.1, 0.1)
CRP	309	-0.6	312	-0.6	0.06 (-0.2, 0.3)
DAS28-CRP	309	-2.7	312	-2.7	-0.01 (-0.2, 0.2)
DAS28-ESR	309	-3.1	312	-3.1	-0.03 (-0.2,0.2)

Source: Statistical Reviewer
[1] Number of patients with complete data included in analysis
[2] Mean difference between CT-P17 and EU-Humira and 95% confidence interval based on a linear regression model adjusted for geographic region and disease activity by simplified disease activity index (SADI) at screening as covariates.

The difference in means for Hybrid ACR responses comparing CT-P17 with EU-Humira were numerically similar at weeks 2, 4, 8, 12, 16, 20 and 24 (**Table 19**).

Table 19: Mean Changes from Baseline and Treatment Difference for Hybrid ACR Score over Time in Study CT-P17 3.1 (ITT Population)

Weeks	CT-P17 (N=324)		EU-Humira (N=324)		Difference (95% CI)[2]
	N[1]	Mean	N[1]	Mean	

Week 2	314	22.1	318	21.1	1.1 (-1.7, 3.9)
Week 4	314	33.5	319	33.8	-0.1 (-3.7, 3.4)
Week 8	313	43.0	318	44.1	-0.9 (-4.6, 2.9)
Week 12	311	49.8	315	50.3	-0.2 (-4.1, 3.6)
Week 16	307	53.7	312	54.1	-0.002 (-3.8, 3.8)
Week 20	305	59.0	310	58.2	1.2 (-2.6, 4.9)
Week 24	303	59.0	308	59.8	-0.5 (-4.3, 3.4)

Source: Statistical Reviewer
[1] Number of patients with complete data included in analysis
[2] Mean difference between CT-P17 and EU-Humira and 95% confidence interval based on a linear regression model adjusted for geographic region and disease activity by simplified disease activity index (SADI) at screening as covariates.

Other Clinical Endpoints

The other secondary efficacy endpoints including the proportion of patients with a good or moderate response (EULAR [CRP] and [ESR]), CDAI, SDAI and SF-36 scores were similar between the CT-P17 and EU-approved Humira treatment groups during Treatment Period 1.

Additional Analyses

The reviewer performed a site analysis and detected a site (SITEID = “2516”, n = 52) in which the entire patients were ACR20 responders at Week 24. To evaluate whether the primary analysis result has been driven by the site, the reviewer performed additional analyses.

The primary analysis excluding the site was performed and the resulting 90% confidence interval (-5.8%, 5.3%) fell within the prespecified similarity margin of (-12%, 15%). Furthermore, the ACR components at Week 24 were compared between groups excluding the site, however, no meaningful difference was found between the groups within each ACR20 component (**Table 20**). Based on the additional analyses, the suspected site did not appear to have impacted the primary analysis result of therapeutic similarity between CT-P17 and EU-approved Humira.

Table 20: Mean Changes from Baseline and Treatment Difference for ACR Components at Week 24 Excluding a Site (SITEID = 2516) in Study CT-P17 3.1 (ITT Population)

Parameter	CT-P17 (N=324)		EU-Humira (N=324)		Difference (95% CI)[2]
	N[1]	Mean	N[1]	Mean	
Tender Joint Count of 68 Joints	281	-15.5	288	-14.8	-0.7 (-2.3, 1.0)
Swollen Joint Count of 68 Joints	281	-11.8	288	-11.6	-0.2 (-1.3, 0.9)

Patient's Assessment of Pain	281	-41.5	288	-43.7	2.3 (-2.2, 6.7)
Patient's Global Assessment of Disease Activity	281	-41.4	288	-43.0	1.7 (-2.7, 6.0)
Physician's Global Assessment of Disease Activity	281	-46.8	288	-47.2	0.5 (-2.9, 3.8)
HQA Estimate of Physical Ability	281	-0.6	288	-0.6	0.04 (-0.1, 0.1)
CRP	281	-0.6	288	-0.7	0.03 (-0.3, 0.3)

Source: Statistical Reviewer
[1] Number of patients with complete data included in analysis
[2] Mean difference between CT-P17 and EU-Humira and 95% confidence interval based on t-test with equal variance.

6.3. Review of Safety Data

6.3.1. Methods

Clinical Studies Used to Evaluate Safety

The safety database for the current submission was comprised of data from 1,228 subjects from the five clinical studies and included 488 healthy male and female subjects (Studies CT-P17 1.1 and 1.3), 30 healthy male subjects (Study CT-P17 1.2), 648 RA subjects (Study CT-P17 3.1) and 62 RA subjects (Study CT-P17 3.2) who were exposed to at least one dose of CT-P17, US-Humira, or EU-Humira. Of these, 297 healthy subjects and 538 RA subjects were exposed to CT-P17.

The review of safety in this review is focused on Study CT-P17 3.1 given the ability to directly compare the relative safety of CT-P17 to EU-Humira. Due to the design limitations of the remaining four studies (e.g., single dosing), analyses of these safety data will not be presented here; however, review of the safety data was performed for these studies and did not reveal any meaningful differences between CT-P17 and when compared to US-licensed Humira or EU-Humira.

The safety database submitted for CT-P17 3.1 included a total of 648 participants who were initially randomized to receive at least one dose of CT-P17 (n=324) or EU-Humira (n=324) through Week 24. For Treatment Period II (at the conclusion of Week 24) 303 subjects initially randomized to CT-P17 were continued on CT-P17, while the subjects initially randomized to EU-Humira were randomized to either continue treatment with EU-Humira (n=153) or to receive treatment with CT-P17 (n=152).

The Safety Population for Study CT-P17 3.1 was defined as any subject who received at least one dose of study drug. The sensitivity of the subject population enrolled in Study CT-P17 3.1 was adequate to identify potential differences in comparative safety between CT-P17 and EU-Humira. The size and the quality of the safety database is sufficient to confidently demonstrate no clinically meaning differences.

For each treatment period during Study CT-P17 3.1, most subjects in each treatment arm had study drug administered as planned. For all scheduled dose weeks, the proportions of subjects who had the dose administered were similar among the treatment groups.

During Treatment Period I, the mean ± SD total number of doses received up to Week 24 was similar between the CT-P17 and EU-Humira treatment groups 12.5±1.79 and 12.5±1.85 doses, respectively.

During Treatment Period II, the mean ± SD total number of doses received from Week 26 to Week 48 was similar among the CT-P17 maintenance arm (11.6±1.57), EU-Humira maintenance arm (11.8±1.01), and switched to CT-P17 treatment groups (11.6±1.72).

For the combined Treatment Periods, the mean ± SD total number of doses received was similar between the CT-P17 and EU-Humira treatment groups (23.4±4.74 and 23.5±4.74 doses, respectively). The mean total number of doses received was also similar among the second randomization groups doses in the CT-P17 maintenance, Humira maintenance, and switched to CT-P17 groups (data not shown).

Categorization of Adverse Events

Safety assessments were performed on AEs, AEs of special interest (AESI), immunogenicity, hypersensitivity monitoring, vital sign and weight measurement, ECGs, physical examination findings, chest X-ray, hepatitis B/hepatitis C and HIV status, pregnancy testing, clinical laboratory analyses, local site pain, signs and symptoms of TB, and prior and concomitant medications monitored throughout the study.

At each visit, subjects were questioned about AEs and concomitant medications and were monitored for clinical signs and symptoms of TB.

An AE was defined as any untoward medical occurrence in a subject enrolled into the study regardless of its causal relationship to study drug. Subjects were instructed to contact the investigator at any time if any symptoms developed. Any new condition noted at Screening would be regarded as an AE, but not a treatment-emergent AE (TEAE).

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

- Resulted in discontinuation from the study
- Required treatment or any other therapeutic intervention

- Required further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)
- Were associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact

If the subject's RA worsened temporarily, disease aggravation was to be captured as the AE term. However, if disease had worsened continuously in the judgment of the investigator (e.g., worsened for >8 weeks), that was considered disease progression and not disease aggravation.

An AESI was reported using the same process as for AEs and included:

- Injection site reactions
- Hypersensitivity/allergic reactions
- Infection
- Malignancy

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

- Results in death
- Was immediately life threatening
- Required subject hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Congenital anomaly/birth defect

Important medical events that did not result in death, were life threatening, or required hospitalization was considered SAEs when, based upon appropriate medical judgment, may have jeopardized the subject or required medical or surgical intervention to prevent one of the outcomes listed in this definition.

All AEs reported or observed during the study were recorded. Information included drug treatment, dose, event term, time of onset, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, action taken with study drug, any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states were reported.

All AEs were recorded according to the CTCAE v5.0. The Medical Dictionary for Regulatory Activities (MedDRA) and used to code all AEs. Any medical condition that was present at the time that the subject was screened but did not worsen was not be reported as an AE; however, had the medical condition deteriorated at any time during the study, it was subsequently recorded as an AE.

The investigator's assessment of an AE's relationship to study drug was part of the documentation process, but did not a factor in determining what was or was not reported in the study. The severity and the relationship or association of the study drug in causing or contributing to the AE was also characterized.

The overall approach taken by the Applicant for categorizing AEs was reasonable and keeping with current standards and practices.

6.3.2. Major Safety Results

Relevant Characteristics of the Population Evaluated for Safety

As shown in Table 15, the relevant characteristics of the subject population evaluated for the safety review is discussed were similarly balanced between treatment arms. Demographic and disease-related characteristics are representative of the rheumatoid arthritis population of patients who are eligible to be treated with adalimumab.

Deaths

No deaths were reported in any of the CT-P17 clinical studies.

Treatment Emergent Adverse Events

SERIOUS ADVERSE EVENTS

A total of 34 SAEs were reported in 31 (5%) subjects during Treatment Period I with 12 CT-P17-treated subjects compared to 19 EU-Humira-treated subjects.

The most frequently reported SAEs by SOC were infections and infestations (CT-P17 [n=4] vs. EU-Humira [n=7]). Basing frequency on PT terminology, no SAEs were reported for more than one subject in either treatment arm.

The majority of SAEs were CTCAE grade 3 in intensity with six events of grade 4 SAEs reported for four subjects: CT-P17 subject (n=1) reported hepatic failure, gastroenteritis rotavirus, and acute kidney injury; CT-P17 subject (n=1) reported injury; and neutropenia was reported for one subject each from both the CT-P17 and EU-Humira groups.

Table 21. Serious Adverse Events by System Organ Class and Preferred Term (Treatment Period I)

System Organ Class Preferred Term	CT-P17 (n=324)	Humira (n=324)
	Number (%) of subjects	
Blood and Lymphatic System Disorders Neutropenia	1 (<1) 1 (<1)	1 (<1) 1 (<1)
Cardiac Disorders Supraventricular tachycardia	0 0	1 (<1) 1(<1)
Eye Disorders Vitreous hemorrhage	0 0	1 (<1) 1(<1)
Gastrointestinal Disorders	1 (<1)	0

Abdominal pain	1(<1)	0
Hepatobiliary Disorders	2 (1)	0
Hepatic failure	1 (<1)	0
Nonalcoholic fatty liver disease	1 (<1)	0
Infections and Infestations	4 (1)	7 (2)
Bronchitis	0	1 (<1)
Cellulitis	1 (<1)	0
Chronic tonsillitis	0	1 (<1)
Epididymitis	0	1 (<1)
Erysipelas	1 (<1)	0
Gastrointestinal rotavirus	1 (<1)	0
Lower respiratory tract infection	0	1 (<1)
Otitis media	1 (<1)	0
Pulmonary TB	0	1 (<1)
Pyelonephritis	0	1 (<1)
TB	0	1 (<1)
Injury, Poisoning, and Procedural Complications	2 (1)	1 (<1)
Femur fracture	0	1 (<1)
Injury	1 (<1)	0
Skin laceration	1 (<1)	0
Musculoskeletal and Connective Tissue Disorders	0	2 (1)
Myositis	0	1 (<1)
Rheumatoid arthritis	0	1 (<1)
Neoplasms Benign, Malignant and Unspecified	2 (1)	1 (<1)
Benign muscle neoplasm	1 (<1)	0
Breast cancer	1 (<1)	0
Uterine leiomyoma	0	1 (<1)
Nervous System Disorders	1 (<1)	1 (<1)
Amyotrophic lateral sclerosis	1 (<1)	0
Syncope	0	1 (<1)
Renal and Urinary Disorders	1 (<1)	0
Acute kidney injury	1 (<1)	0
Respiratory, Thoracic, and Mediastinal Disorders	0	1 (<1)
Rheumatoid lung	0	1 (<1)
Surgical and Medical Procedures	0	2 (1)
Cataract operation	0	1 (<1)
Polypectomy	0	1 (<1)
Vascular Disorders	0	1 (<1)
Hypertension	0	1 (<1)

Source: Applicant's ctp1731-body, Page 198, Table 12-13

A total of 15 SAEs were reported in 14 (2%) subjects during Treatment Period II comprising six CT-P17-treated subjects, three EU-Humira maintenance subjects, and five subjects who switched to the CT-P17 arm.

The most frequently reported SAE for subjects in the CT-P17 maintenance group was pneumonia (n=2). No other SAEs were reported for more than one subject in each treatment arm.

The majority of SAEs were CTCAE grade 3 in intensity with two events of grade 4 SAEs being reported for two subjects, a single case of neutropenia in a subject receiving CT-P17 maintenance and a single case of extradural hematoma for one subject in the EU-Humira maintenance arm.

Table 22. Serious Adverse Events by System Organ Class and Preferred Term (Treatment Period I)

System Organ Class Preferred Term	CT-P17 Maintenance (N=303)	Humira Maintenance (N=152)	Switch to CT-P17 (N=152)
	Number (%) of subjects		

Blood and Lymphatic System Disorders	1 (<1)	0	0
Neutropenia	1 (<1)	0	0
Cardiac Disorders	0	1 (1)	0
Angina unstable	0	1 (1)	0
Eye Disorders	0	0	1 (1)
Retinal vein thrombosis	0	0	1 (1)
Infections and Infestations	2 (1)	0	1 (1)
Breast abscess	0	0	1 (1)
Pneumonia	2 (1)	0	0
Injury, Poisoning, and Procedural Complications	2 (1)	1 (1)	0
Extradural hematoma	0	1 (1)	0
Limb crushing injury	1(<1)	0	0
Tendon rupture	1(<1)	0	0
Neoplasms Benign, Malignant and Unspecified	0	1 (1)	0
Basal cell carcinoma	0	1 (1)	0
Nervous System Disorders	0	0	1 (1)
Carotid artery occlusion	0	0	0
Ischemic stroke	0	0	1 (1)
Reproductive system and breast disorders	1 (<1)	0	1 (1)
Endometrial hyperplasia	1 (<1)	0	0
Endometriosis	0	0	1 (1)
Respiratory, Thoracic, and Mediastinal Disorders	1 (<1)	0	0
Rheumatoid lung	1 (<1)	0	0
Source: Applicant's ctp1731-body, Page 200, Table 12-14			

Overall, the types and frequency of SAEs were similar between treatment arms and consistent with the known safety profile of adalimumab. There were no unique safety signals identified.

ADVERSE EVENTS

A summary of AEs during both Treatment Periods is summarized in Table 23.

Table 23. Summary of Adverse Events (Treatment Periods I and II)

	Treatment Period I	Treatment Period II			
	CT-P17 (N=324)	EU-Humira (N=324)	CT-P17 Maintenance (N=303)	EU-Humira Maintenance (N=152)	Switched to CT-P17 (N=152)
Adverse events, n (%)	218 (67)	229 (71)	204 (67)	105 (69)	107 (70)
Serious adverse events, n (%)	17 (5)	27 (8)	10 (3)	10 (7)	12 (8)
Adverse events leading to study drug discontinuation	10 (3)	17 (5)	3 91)	3 (2)	5 (3)
Adverse events of Special Interest					
Hypersensitivity/allergic reaction	3 (1)	5 (2)	3 (1)	2 (1)	1 (1)
Injection site reactions	17 (50	24 (7)	16 (5)	12 (8)	11 (7)
Infection	133 (41)	152 (47)	125 (41)	74 (49)	68 (45)
Malignancy	1 (<1)	1 (<1)	0	1 (0)	0
Deaths	0	0	0	0	0

Source: Applicant's ctp1731-body, Page 186, Table 12-6

A total of 1531 AEs were reported in 447 (69%) subjects and the proportion of subjects were similar between the CT-P17 and EU-Humira treatment groups (n=218, 67% vs. n=229, 71%, respectively). Similarly, the proportion of AEs was similar between the CT-P17 maintenance, EU-Humira maintenance and switched to CT-P17 groups (n=204, 67%, n=105, 69%, and n=107, 70%, respectively). The majority of AEs were grade 1 or grade 2 in severity.

Adverse events of special interest classified as hypersensitivity/allergic reactions were reported for three (1%) and five (2%) subjects in the CT-P17 and EU-Humira treatment groups, respectively; and three (1%), two (1%), and one (1%) subjects in the CT-P17 maintenance, EU-Humira maintenance and switched to CT-P17 groups, respectively. Those AESI reported as injection site reactions were reported for 17 (5%) and 24 (7%) subjects in the CT-P17 and EU-Humira treatment groups, respectively, and 16 (5%), 12 (8%), and 11 (7%) subjects in the CT-P17 maintenance, EU-Humira maintenance and switched to CT-P17 groups, respectively.

Adverse events of special interest classified as infections were reported for 133 (41%) and 152 (47%) subjects in the CT-P17 and EU-Humira treatment groups, respectively; and 125 (41%), 74 (49%), and 68 (45%) subjects in the CT-P17 maintenance, EU-Humira maintenance and switched to CT-P17 groups, respectively. Those AESI

classified as malignancy was reported for one subject each in the CT-P17 treatment, EU-Humira treatment, and EU-Humira maintenance groups.

All AEs reported for 5% or more of subjects in any treatment group in during both Treatment Periods are summarized by Preferred Term in Table 24.

Table 24. Adverse Events Reported for ≥5% of Subjects in Any Treatment Group using Preferred Term (Treatment Periods I and II)

	Treatment Period I	Treatment Period II			
Preferred Term	CT-P17 (N=324)	EU-Humira (N=324)	CT-P17 Maintenance (N=303)	EU-Humira Maintenance (N=152)	Switched to CT-P17 (N=152)
Upper respiratory tract infection, n (%)	23 (7)	37 (11)	22 (7)	18 (12)	16 (11)
Nasopharyngitis, n (%)	23 (7)	26 (8)	22 (7)	16 (11)	8 (5)
Neutropenia, n (%)	21 (7)	24 (7)	20 (7)	10 (7)	14 (9)
Urinary tract infection, n (%)	22 (7)	21 (7)	18 (6)	9 (6)	10 (7)
Injection site reaction, n (%)	17 (5)	24 (7)	16 (5)	12 (8)	11 (7)
Alanine aminotransferase increased, n (%)	17 (5)	22 (7)	15 (5)	9 (6)	8 (5)
Pharyngitis, n (%)	16 (5)	17 (5)	15 (5)	9 (6)	8(5)
Latent tuberculosis, n (%)	12 (4)	12 (4)	12 (4)	2 (1)	10 (7)
Leukopenia, n (%)	14 (4)	12 (4)	12 (4)	2 (1)	10 (7)
Aspartate aminotransferase increased, n (%)	8 (3)	15 (5)	8 (3)	5 (3)	9 (6)

Source: Applicant's ctp1731-body, Page 188, Table 12-9

A higher proportion of subjects were observed to have elevated alanine aminotransferase levels and leukopenia in the switched to CT-P17 group (n=15, 10% and n=10, 7% subjects, respectively) compared to the CT-P17 maintenance and EU-Humira maintenance groups.

A total of 447 (69%) subjects experienced at least one AE during either Treatment Period with similar proportions between the CT-P17 and EU-Humira treatment groups (n=218, 67% and n=229, 71%, respectively); and in the CT-P17 maintenance, EU-Humira maintenance and switched to CT-P17 groups (n=204, 67%, n=105, 69%, and n=107, 70%, respectively).

The most frequently reported AEs for subjects in the CT-P17 treatment group were upper respiratory tract infection and nasopharyngitis (n=23, 7%) followed by urinary tract infection (n=22, 7%). The most frequently reported AEs for subjects in the EU-Humira treatment group were upper respiratory tract infection (n=37, 11%) followed by

nasopharyngitis (n=26, 8%). The most frequently reported AEs for subjects in the CT-P17 maintenance group were upper respiratory tract infection and nasopharyngitis (n=22, 7%) followed by neutropenia (n=20, 7%). The most frequently reported AEs for subjects in the EU-Humira maintenance group were upper respiratory tract infection (n=18, 12%) followed by nasopharyngitis (n=16, 11%). The most frequently reported AEs for subjects in the switched to CT-P17 group were upper respiratory tract infection (n=16, 11%) followed by alanine aminotransferase increased (n=15, 10%).

Overall, the types and frequency of AEs were similar between treatment arms and consistent with the known safety profile of adalimumab, supporting the demonstration of no clinically meaningful differences between CT-P17 and US-Humira. There were no unique safety signals identified.

Dropouts and/or Discontinuations

A total of 27 (4%) subjects experienced at least one AE leading to study drug discontinuation with similar proportions of subjects between the CT-P17 and EU-Humira treatment groups (n=10, [3%] and n=17, [5%], respectively), and among CT-P17 maintenance, EU-Humira maintenance, and switched to CT-P17 groups (n=3, [1%], n=3, [2%], and n=5, [3%] subjects, respectively).

Fifteen (2%) subjects who discontinued the study treatment in Treatment Period I was due to an adverse event (CT-P17: n=7; EU-Humira: n=8) and 12 subjects who have discontinued the study treatment in Treatment Period II due to an adverse event from the CT-P17 maintenance group (n=3), EU-Humira maintenance group, (n=3) and from the switched to CT-P17 group (n=6).

One subject in the EU-Humira treatment group who switched to CT-P17 reported an AE of latent tuberculosis based on the positive IGRA test. The AE of latent tuberculosis was identified and classified during Treatment Period I; however, the subject was considered to have discontinued the study treatment during Treatment Period II as the subject discontinued the study treatment after the second randomization.

Similarly, one subject initially randomized to the EU-Humira treatment group was reported to have an AE of osteoarthritis and to the EU-Humira maintenance group but discontinued the study after the second randomization.

Overall, the numbers of subjects and reasons for discontinuation from study drug was similar between treatment arms in both Treatment Periods.

6.4. Clinical Conclusions on Immunogenicity

Analysis of the immunogenicity data from the single PK similarity study CT-P17 1.1 demonstrated that at the end of the study the overall incidence of ADA formation in

healthy subjects was similar between CT-P17, US-Humira and EU-Humira (95%, 92%, and 91%, respectively). Similarly, at the same time point, the overall incidence of NAb formation was also similar between the treatment arms (72%, 80, and 76%, respectively).

Study CT-P17 3.1 is considered the more clinically relevant study regarding immunogenicity given that RA subjects were treated with multiple 40 mg SC doses of CT-P17 or EU-Humira. Analysis of the data demonstrated that the incidence of ADA was numerically lower in CT-P17-treated subjects compared to EU-Humira-treated subjects (29% and 36%, respectively). Similarly, subjects treated with CT-P17 also developed lower proportions of NAb compared to the EU-Humira group (26% and 32%, respectively). In subjects who switched from EU-Humira to CT-P17 at Week 24, the ADA positivity rate remained similar as compared to subjects maintained on CT-P17 or EU-Humira. The ADA and NAb formation were not increased following the single transition from EU-Humira to CT-P17, with the incidence of ADA and NAb (45% and 45%, respectively).

While these data show that the ADA positive rate in subjects receiving CT-P17 was numerically lower than subjects receiving EU-Humira, the difference overall is considered clinically insignificant.

In subjects who developed ADAs, a time-dependent NAb development was observed. Almost all ADA positive subjects developed NAb after 16 to 20 weeks of treatment; however, no difference was observed between CT-P17 and EU-Humira. The NAb positivity rate remained similar to subjects maintained on CT-P17 and EU-Humira in subjects switched from EU-Humira to CT-P17 after Week 24.

Further analysis by Drs. Liu and Ji demonstrated that NAb had no effect on pharmacokinetic, pharmacodynamic or clinical efficacy responses and supports the conclusion of similar immunogenicity response between CT-P17 and EU-Humira and the demonstration of no clinically meaningful differences between CT-P17 and US-Humira. The reader is referred to Section 5.4 for a detailed discussion regarding the immunogenicity related to the CT-P17 development program.

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6.5. Extrapolation

The collective evidence from the comparative clinical studies that evaluated PK, immunogenicity, safety and efficacy, and the data that established the scientific bridge to justify the relevance of clinical data with EU-Humira as the comparator, supports a demonstration of no clinically meaningful differences between CT-P17 and US-Humira

in the studied indication (RA). In addition to the RA indication, the Applicant is seeking licensure for following six indications, for which US-Humira has been previously approved and for which CT-P17 has not been directly studied:

1. Juvenile Idiopathic Arthritis (JIA) in patients 2 years of age and older
2. Psoriatic Arthritis (PsA)
3. Ankylosing Spondylitis (AS)
4. Crohn's Disease (CD) in patients 6 years of age and older
5. Ulcerative Colitis (UC) in adults
6. Rheumatoid arthritis (RA)

The Applicant provided a justification for extrapolation of data and information submitted in the application to support licensure of CT-P17 as a biosimilar for each indication for which licensure is sought and for which US-Humira has been previously approved.

First, the Applicant's extensive analytical characterization data support a demonstration that CT-P17 is highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components. In addition, the data support a demonstration there are no clinically meaningful differences between CT-P17 and US-licensed Humira in terms of safety, purity and potency based on similar clinical pharmacokinetics, and similar efficacy, safety, and immunogenicity in patients with RA.

Further, the additional points considered in the scientific justification for extrapolation of data and information to support licensure of CT-P17 for the treatment of JIA in patients 2 years of age and older, RA, PsA, AS, CD in patients 6 years of age and older, and UC in adults, include:

- Similar PK was demonstrated between CT-P17 and US-Humira as discussed in the section on Clinical Pharmacology. Importantly, CT-P17 was demonstrated to be highly similar to US-Humira, as discussed in the section on CMC/Product Quality, and there are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between CT-P17 and US-Humira in the indications sought for licensure. Thus, a similar PK profile would be expected between CT-P17 and US-Humira in patients across all the indications being sought for licensure.

- In general, immunogenicity of US-Humira was affected primarily by the dosing regimen and the use of concomitant immunosuppressive therapy across different indications rather than by patient population, and the results were influenced by the type of immunoassay used.[4] As stated elsewhere in this document, the Agency has concluded that there are sufficient data to support similar immunogenicity between CT-P17 and EU-Humira with repeat dosing in patients with RA, and between CT-P17, US- Humira, and EU-Humira, after a single dose in healthy subjects. Accordingly, similar immunogenicity would be

expected between CT-P17 and US-Humira in patients with JIA, RA, PsA, AS, CD in patients 6 years of age and older, and UC in adults.

- The Applicant demonstrated that there are no clinically meaningful differences between CT-P17 and EU-Humira in patients with RA, and between CT-P17, US-Humira, and EU- Humira following single doses in healthy subjects. Additionally, in controlled clinical studies of US-Humira submitted to support its approval, as described in the approved labeling, the types of adverse events and their rates were similar across indications. The foregoing, coupled with the demonstration of analytical and PK similarity between CT-P17 and US-Humira, support the conclusion that a similar safety profile would be expected between CT-P17 and US-Humira in patients with JIA, RA, PsA, AS, CD in patients 6 years of age and older, and UC in adults.

- The Applicant addressed each of the known and potential mechanisms of action of US-Humira and submitted data to support the conclusion that CT-P17 and US-licensed Humira have the same mechanisms for each of the sought indications, to the extent that the mechanisms of action are known or can reasonably be determined.

Therefore, based on the above considerations, DRTM, DDD, and DG review teams have concluded (see also Sections 6.5.1, 6.5.2, and 6.5.3) that the Applicant has provided adequate data and information to support licensure of CT-P17 for each of the following indications for which US-licensed Humira has been previously licensed and for which the Applicant is seeking licensure of CT-P17: RA, JIA in patients 2 years and older, PsA, AS, PsO, CD in patients 6 years and older, and UC in adults.

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6.5.1. Division of Rheumatology and Transplant Medicine (DRTM)

The Applicant provided a justification for extrapolation of data and information submitted in the application to support licensure of CT-P17 as a biosimilar for each indication for which licensure is sought and for which US-Humira has been previously approved.

The Applicant conducted a comparative clinical study with CT-P17 in patients with rheumatoid arthritis. They are also seeking licensure for other indications for which US-licensed Humira has been previously licensed, including, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and juvenile idiopathic arthritis. Although the Applicant has not conducted clinical studies in these other indications, they have

provided adequate scientific justification to support extrapolation of the data and information submitted, to support licensure under section 351(k) of the PHS Act of as a biosimilar for rheumatoid arthritis, plaque psoriasis, ankylosing spondylitis, psoriatic arthritis, and juvenile idiopathic arthritis in patients 2 years and older (see Section 6.5).

DRTM has determined that the Applicant has provided sufficient scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of data and information submitted, including clinical data from the studied population to support extrapolation of data and information submitted by the Applicant to support licensure under section 351(k), of CT-P17 as a biosimilar for the following rheumatologic indications:

- Rheumatoid Arthritis (RA): Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
- Psoriatic Arthritis (PsA): Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
- Ankylosing Spondylitis (AS): Reducing signs and symptoms in adult patients with active AS.
- Juvenile Idiopathic Arthritis (JIA): Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 years of age and older.

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6.5.2. Division of Gastroenterology

Executive Summary: Consistent with the principles of the FDA Guidance - Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015)[4], 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-P17 as a biosimilar, under section 351(k) of the PHS Act, for the inflammatory bowel disease (IBD) indications of Crohn's disease (CD) in patients 6 years and above, and ulcerative colitis (UC) in adults (non-studied indications). The scientific justification based on the mechanism of action, pharmacokinetics, immunogenicity and safety supporting this conclusion are summarized in the following paragraphs.

Mechanism of Action: The mechanisms of action of adalimumab that are relevant to rheumatoid arthritis (RA), the studied clinical study population, are also relevant to

[4] Guidance for Industry – Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

inflammatory bowel disease (IBD) (i.e., CD and UC). The Applicant provided data to support that CT-P17 has the same known and potential mechanisms of action as US-Humira, which supports extrapolation to indications not directly studied in the CT-P17 clinical program. Adalimumab belongs to the pharmacologic class of tumor necrosis factor alpha (TNF-α) blockers. Adalimumab neutralizes the biological activity of TNF-α by binding with high affinity to the soluble (s) (sTNF-α) and transmembrane (tm) (tmTNF-α) forms of TNF-α and inhibits binding of TNF-α with its receptors. Similar to the studied indication (RA), TNF-α plays a central role in the pathogenesis of IBD. TNF-α inhibition is important in treating the disease, as evidenced by the efficacy of approved TNF-α inhibitors in the treatment of IBD. In addition, the efficacy of adalimumab in the treatment of IBD is thought to involve reverse signaling via binding to tmTNF-α, and other plausible mechanisms of action involving the Fc region of the antibody.[5,6] Table 25 summarizes the known and potential mechanisms of action of US-licensed Humira. Binding to sTNF-α and tmTNF-α involves the fragment antigen-binding (Fab) region of the antibody, while the other plausible mechanisms of action involve the fragment crystallizable (Fc region) region of the antibody.

Table 25 Known and Potential Mechanisms of Action of US-Humira

MOA of US-Humira	RA	AS	PsA	PsO	CD	UC
Mechanisms involving the Fab (antigen binding) region:						
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF	Known	Known	Known	Known	Likely	Likely
Reverse (outside-to-inside) signaling via binding to tmTNF	-	-	-	-	Likely	Likely
Mechanisms involving the Fc (constant) region:						
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible
Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible
Induction of regulatory macrophages in mucosal healing	-	-	-	-	Plausible	Plausible

ADCC: antibody-dependent cellular cytotoxicity; AS: ankylosing spondylitis; CD: Crohn's disease; CDC: complement-dependent cytotoxicity; MOA: mechanism of action; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; UC: ulcerative colitis; sTNF: soluble TNF; tmTNF: transmembrane TNF

Source: FDA summary of current literature on the topic of mechanisms of action of TNF inhibitors[5,6,7]

The biological activities of CT-P17 and US-Humira were evaluated by a comprehensive set of comparative functional and binding assays. The product quality reviewers concluded that the comparative analytical assessment was acceptable. Data for TNF-α binding and neutralization, the primary function of adalimumab, as well as other mechanisms of action, such as reverse signaling, antibody dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and induction of regulatory macrophages support the determination that CT-P17 and US-Humira are

[5] Oikonomopoulos A, et al., Current Drug Targets 2013; 14:1421-32
[6] Tracey D, et al., Pharmacology & Therapeutics 2008; 117:244–79
[7] Olesen, C.M, et.al., Pharmacology & Therapeutics 159 (2016), 110-119.

highly similar. These data support the conclusion that CT-P17 and US-Humira utilize the same mechanism(s) of action, to the extent such mechanism(s) are known.

Pharmacokinetics (PK): Study CT-P17 1.1 was a randomized, double-blind, parallel group, single dose, PK similarity study conducted in healthy adult male and female subjects. The clinical pharmacology reviewers concluded that the data from study CT-P17 1.1 support a demonstration of PK similarity of CT-P17 to US-Humira in healthy subjects (refer to Section 5 Clinical Pharmacology Evaluation and Recommendations). Available data on US-Humira do not indicate any major differences in PK based on disease state. Therefore, it is reasonable to conclude that PK for CT-P17 is expected to be similar between patients with RA (the studied population) and those with IBD. In addition, it should be noted that the PK of adalimumab products is also influenced by immunogenicity. Specifically, the clearance of adalimumab has been shown to be higher in patients who developed anti-drug-antibodies (ADA). Immunogenicity considerations are discussed further below.

Immunogenicity: In the CT-P17 development program, immunogenicity was evaluated in populations that were considered sensitive for detecting meaningful differences (RA patients and healthy subjects). Immunogenicity was found to be similar when comparing CT-P17 and US-Humira in the PK similarity study CT-P17 1.1 in healthy subjects, and between CT-P17 and EU-Humira in the comparative clinical study CT-P17 3.1 conducted in patients with RA.

Specifically, the rates of binding and neutralizing anti-drug antibodies were found to be similar between CT-P17 and US-Humira or EU-Humira in these studies. These results support a demonstration of no clinically meaningful differences between CT-P17 and US-Humira. In the clinical study CT-P17 3.1, patients who received EU-Humira were re-randomized to either continue on EU-Humira or switch to CT-P17, thus providing information on the effect of switching between the two treatments. The single transition was used to specifically assess potential risks with regard to the safety and immunogenicity as a result of switching from EU-Humira to CT-P17. There were no meaningful differences in the rates of binding and neutralizing antidrug antibodies in those subjects that underwent a single transition from EU-Humira to CT-P17, compared to those that remained on their randomized treatment (EU-Humira or CT-P17). Therefore, it is reasonable to conclude that immunogenicity in patients with IBD receiving CT-P17 would be similar to that observed in patients with IBD receiving US-Humira.

Safety: The safety of CT-P17 compared to EU-Humira was assessed in comparative clinical study (CT-P17 3.1) conducted in patients with RA, and supported by a single dose, PK similarity study (CT-P17 1.1) conducted in healthy subjects. Safety assessments in the two clinical studies included adverse events (AEs), physical examinations, vital signs, electrocardiograms (ECGs), clinical laboratory testing, and immunogenicity assessments. As described in Section 6.3– Review of Safety Data, the data overall support a similar safety profile between the CT-P17 and EU-Humira, and there were no meaningful differences in the frequency of TEAEs, SAEs, and events

leading to discontinuation of study drug. In addition, as previously noted, a single transition from EU-Humira to CT-P17 was assessed as part of the study CT-P17 3.1. No meaningful differences in the incidence of adverse events, including hypersensitivity, were observed in patients with RA that underwent a single transition from EU-Humira to CT-P17, compared to those that remained on their randomized treatment (CT-P17 or EU-Humira). In controlled clinical studies of US-licensed Humira, as described in the approved labeling, the types of adverse events and their rates were similar across indications. Since the safety profile of CT-P17 has been shown to be similar to that of EU-Humira in patients with RA, combined with an adequate PK bridging between US-Humira and EU-Humira from the healthy subject study CT-P17 1.1 and the similar product quality attributes, PK, and immunogenicity, we expect that the safety profile in the IBD population is unlikely to be different from that observed in patients with RA.

Pediatric CD: The following rationale supports extrapolation to the pediatric CD indication (note that orphan drug exclusivity for pediatric CD expired on September 23, 2021):

- The mechanisms by which adalimumab exerts its therapeutic effect are expected to be the same in adults and in pediatric CD patients. Together with the demonstrated structural and functional similarity between CT-P17 and US-Humira, the mechanisms of action of CT-P17 are not expected to be different from that of US-Humira in pediatric CD, to the extent that the mechanisms are known or can be reasonably determined.

- Adalimumab concentrations are similar in adult and pediatric CD patients (Humira USPI, 2021). Together with the demonstrated 3-way PK similarity (CT-P17 vs. US-Humira vs. EU-Humira) in healthy volunteers, and between CT-P17 vs. EU-Humira in patients with RA, the PK following CT-P17 are not expected to be different to that of US-Humira in pediatric CD patients.

- Immunogenicity rates of US-Humira were comparable between adult and pediatric CD patients (Humira USPI, 2021). Together with the comparable immunogenicity in healthy volunteers (CT-P17 vs. US-Humira vs. EU-Humira) and in RA patients (CT-P17 vs. EU-Humira), the immunogenicity of CT-P17 is not expected to be different from that of US-Humira in pediatric CD patients.

- The safety profile of US-Humira was comparable in adult vs. pediatric CD patients (Humira USPI, 2021). Together with the demonstrated comparable safety profile of CT-P17 vs. EU-Humira in adult RA patients, combined with establishment of an adequate scientific bridge to justify the relevance of clinical data using EU-Humira as the comparator, the safety of CT-P17 is not expected to be different from that of US-Humira in pediatric CD patients.

Regulatory Recommendations: DG concludes that sufficient scientific justification was provided to support licensure of CT-P17 for the following indications:

- For the treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.
- For the treatment of moderately to severely active ulcerative colitis in adult patients.

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6.5.3. Division of Dermatology and Dentistry

Executive Summary:

Under section 351(k) of the PHS Act and in accordance with the principles outlined in the Guidance for Industry, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015), the Division of Dermatology and Dentistry (DDD) concludes that the Applicant's scientific justification is sufficient for extrapolating data submitted in the application to support licensure of CT-P17 as a biosimilar for the dermatological indication of moderate to severe plaque psoriasis in adults who are candidates for systemic or phototherapy for which US-licensed Humira has been previously approved. US-licensed Humira is not approved for the treatment of chronic moderate to severe plaque psoriasis in the pediatric population.

Although the Applicant did not conduct a clinical study in plaque psoriasis patients, the Applicant provided adequate scientific justification to substantiate extrapolation of the data and information submitted, to support licensure under section 351(k) of the PHS Act of CT-P17 as a biosimilar for plaque psoriasis.

The comprehensive comparative analytical assessment demonstrated that CT-P17 is highly similar to US-Humira. The collective evidence from the comparative clinical studies that evaluated PK, immunogenicity, safety and efficacy, and the data that established the scientific bridge to justify the relevance of clinical data with EU-Humira as the comparator, supports a demonstration of no clinically meaningful differences between CT-P17 and US-Humira in the studied indication (RA). The known mechanisms of action of adalimumab that are relevant to RA are also considered relevant to plaque psoriasis. Based on the totality of this data and information, as well as the scientific justification as detailed below, it is reasonable to conclude that the assessments conducted in RA subjects who received CT-P17 would be applicable to adult patients with plaque psoriasis.

Extrapolation for the Plaque Psoriasis indication:

CT-P17 has met the statutory requirements for licensure as a biosimilar biological product under section 351(k) of the PHS Act based on, among other things, the data derived from the submitted studies, which sufficiently demonstrated safety, purity, and potency in an appropriate condition of use (RA). The applicant intends to seek licensure

for one or more additional conditions of use for which the reference product has been previously licensed.
To support extrapolation for the non-studied condition of use, plaque psoriasis, for which licensure is sought, scientific justification addressed mechanism(s) of action (MOA), pharmacokinetics (PK), immunogenicity, and toxicity.

The primary **mechanism of action** of US-licensed Humira is direct binding and neutralization of TNF receptor-mediated biological activities. US-licensed Humira binds to both soluble (s) and transmembrane (tm) TNF, impeding TNF binding to receptors TNFR1 and TNFR2 and thus blocking several downstream pro-inflammatory events including the release of serum cytokines (interleukin-6), matrix metalloproteases, and the expression of adhesion molecules responsible for leukocyte migration. The blockage of these events and others is also thought to prevent epidermal cell hyperproliferation responsible for psoriatic skin lesions.[8] The product quality reviewers determined that the data provided by the Applicant demonstrated similar TNF binding and potency to neutralize TNFα, supporting that the primary MOAs of US-licensed Humira and CT-P17 are much the same. The known mechanisms of action of adalimumab that are relevant to RA are also considered relevant to plaque psoriasis.

Available data on US-Humira have not demonstrated any major differences in **pharmacokinetics** based on disease state.[9,10,11] Because similar PK was demonstrated between CT-P17 and US-licensed Humira (as discussed in Section 5 by the Clinical Pharmacology review team), a similar PK profile would be expected for CT-P17 in patients with chronic moderate to severe plaque psoriasis.

- The **immunogenicity** analyses of CT-P17 demonstrated comparable incidences of ADA formation between CT-P17, EU-Humira, and US-Humira in healthy subjects, as well as similar incidences of ADA formation between CT-P17 and EU-Humira in patients with RA. Because a scientific bridge was established to justify the relevance of data generated with EU-Humira, these data support a demonstration of no clinically meaningful differences between CT-P17 and US-Humira. Therefore, it is reasonable to conclude that immunogenicity in plaque psoriasis patients receiving CT-P17 would be similar to that observed in plaque psoriasis patients receiving US-licensed Humira.

[8] Shivani P. Reddy, Elaine J. Lin, Vidhi V. Shah, Jashin J. Wu, Chapter 10 - Adalimumab, Editor(s): Jashin J. Wu, Steven R. Feldman, Mark G. Lebwohl, Therapy for Severe Psoriasis, Elsevier, 2016, Pages 111-126
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[10] Huizinga TWJ, Torii Y, Muniz R. Adalimumab Biosimilars in the Treatment of Rheumatoid Arthritis: A Systematic Review of the Evidence for Biosimilarity. Rheumatol Ther. 2021;8(1):41-61. doi:10.1007/s40744-020-00259-8
[11] Azevedo V, Dela Coletta Troiano Araujo L, Bassalobre Galli N, kleinfelder A, marostica Catolino N, martins Urbano PC. Adalimumab: a review of the reference product and biosimilars. Biosimilars. 2016;6:29-44 https://doi.org/10.2147/BS.S98177

- As indicated above, no clinically meaningful differences were identified between CT-P17 and US-Humira. This assessment was determined by the single-dose PK similarity study (CT-P17 1.1) which compared the PK, immunogenicity, and safety of CT-P17 (PFS), US-licensed Humira (PFS), and EU-approved Humira (PFS) in 312 healthy subjects, the establishment of an adequate analytical and PK bridge with CT-P17, US-Humira and EU-Humira, as well as by the comparative clinical study CT-P17 3.1, which compared the efficacy, safety, immunogenicity, and PK of CT-P17 and EU-approved Humira administered in 648 adults with moderate to severe active RA.

- Overall, the **safety** profiles of CT-P17, US-licensed Humira, and EU-approved Humira, including events of special interest (i.e., serious infections, hypersensitivity reactions, and malignancies) were comparable among the various treatment groups and consistent with the established safety profile of US-licensed Humira. Additionally, during the comparative clinical study, the safety profiles of CT-P17 and EU-approved Humira were similar after the single blind transition from EU-approved Humira to CT-P17 at Week 26. Furthermore, in controlled clinical studies of US-Humira that were submitted to support its approval and as described in the approved labeling, the types and rates of adverse events have been similar across indications. This information, along with the demonstration of analytical similarity between CT-P17 and US-Humira, supports the conclusion that a similar safety profile would be expected between CT-P17 and US-Humira in psoriasis patients.

Conclusion:
DDD 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 submitted in the application to support licensure of CT-P17 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic or phototherapy for which US-licensed Humira has been previously approved.

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Clinical Reviewer	Clinical Team Leader	Deputy Division Director

7. Labeling Recommendations

In view of the recommendation for a Complete Response, final labeling recommendations will be deferred until the next review cycle, if applicable.

7.1. Nonproprietary Name

The Applicant's nonproprietary name, adalimumab-aaty was found to be conditionally accepted by the Agency.

7.2. Proprietary Name

The Applicant's proposed proprietary name for CT-P17, YUFLYMA, has been conditionally approved. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), who concluded that the name is acceptable (DMEPA review dated February 19, 2021).

7.3. Other Labeling Recommendations

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

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

In compliance with 21 CFR Part 54, the Applicant has adequately disclosed financial interests and arrangements with the investigators and sub investigators who participated in covered clinical studies for CT-P17.

Form 3454 is noted (Module 1.3.4, SDN 104) and verifies that no compensation is linked to study outcome. The Principal Investigators and sub investigators did not disclose any proprietary interest to the Applicant.

The covered clinical studies as defined in 21 CFR 54.2 (e) was Study CT-P17 3.1. Refer to Section 13.1of this review [Financial disclosure].

All studies were conducted according to Good Clinical Practice (GCP) as described in the International Conference on Harmonisation (ICH) Guideline E6 and in accordance with the ethical principles outlined in the Declaration of Helsinki. The studies were conducted in compliance with the protocols. Informed consent, protocol, amendments, and administrative letters for the studies received Institutional Review

Board/Independent Ethics Committee approval prior to implementation. Subjects signed informed consent documents. Written informed consent was obtained prior to subjects entering the studies (before initiation of protocol-specified procedures). The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. The investigators conducted all aspects of these studies in accordance with applicable national, state, and local laws of the pertinent regulatory authority.

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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.

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10. Pediatrics

In view of the recommendation for a Complete Response, any recommendations for PREA post-marketing requirement(s) were deferred until the next review cycle.

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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.

12. Comments to Applicant

DEFICIENCY

Facility Inspections:

During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

ADDITIONAL COMMENTS:

We have the following comments/recommendations that are not approvability issues:

Product Quality:

1. Implement (b) (4) validated by bacterial retention study.

2. The endotoxin limit for (b) (4) exceeds the endotoxin limit for release. This may allow for the production of a batch that may meet (b) (4) limits but exceeds the specification for release. Update the endotoxin (b) (4) limit and/or the release specification.

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3. You have provided testing on 10 samples to demonstrate that the full dose is delivered prior to the sound of the second click. However, to ensure that you adequately control the design so that the full dose is always delivered prior to the sound of the second click, please define specifications for the end of injection click timing, and verify the new specification.

4. (b) (4) has provided testing on the PFS-S device's lockout force, however in order to be representative this test should be conducted after simulated shipping on the final finished device with your packaging design. In order to ensure proper functioning of the PFS-S lockout force, provide testing after simulated shipping per ASTM 4169-16, Standard Practice for Performance Testing of Shipping Containers and Systems on your final finished device in the final packaging.

13. Appendices

13.1. Financial Disclosure

Covered Clinical Study: Studies CT-P17 1.1; CT-P17 1.2; CT-P17 1.3; CT-P17 3.1; CT-P17 3.2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 393		
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): 0		
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)): NON-APPLICABLE 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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The Applicant requested Financial Disclosure Statements from 70 Principal Investigators and 323 sub-investigators. There were no principal or sub-investigators who did not return the financial disclosure information. No investigator reported disclosable information.

13.2. Clinical Pharmacology Appendices

13.2.1. Summary of Bioanalytical Method Validation and Performance

Pharmacokinetics

For the Study CT-P17 1.1, CT-P17 3.1, and CT-P17 1.3, serum CT-P17, U.S.-Humira, and EU-Humira concentrations measured using a validated electrochemiluminescence (ECL) (RKAJ8) were suitable for assessment of PK similarity. Both the method validation entitled "RKAJ8" and sample analysis for the study were performed at (b) (4). Table 26 shows the summary of RKAJ8 method performance in quantification of CT-P17, U.S.-Humira and EU-Humira during the method validation.

Table 26 Summary of the bioanalytical method validation and in-study performance for measurement of CT-P17, U.S.-Humira, and EU-Humira

Bioanalytical method validation report name, amendments, and hyperlinks	• RKAJ8 Method Validation Report (Section 5.3.1.4) • RKAJ11 Method Validation Report Addendum 1 (Section 5.3.1.4) • RKAJ11 Method Validation Report Addendum 1 Amendment 1 (Section 5.3.1.4) • RKAJ9 Method Validation Report Addendum 2 (Section 5.3.1.4) • RKAJ9 Method Validation Report Addendum 3 (Section 5.3.1.4)
Method description	• MSD-ECL bridging assay using Biotinylated TNFα and Sulfo-tag-labelled TNFα for measuring CT-P17 and reference products (US-Humira® and EU-Humira®) in human normal serum and RA patient serum samples.
Materials used for standard calibration curve and concentration	• Standard calibrations were prepared by spiking CT-P17 into normal healthy human serum. • Standard concentrations: 50 (anchor), 100, 200, 400, 750, 1400, 2500, 5000, 10000 and 15000 ng/mL
Validated assay range	• 100 to 15000 ng/mL
Material used for quality controls (QCs) and concentration	• Quality controls were prepared by spiking CT-P17 into normal healthy human serum. • Quality controls concentrations: 100 ng/mL (LLOQ), 250 ng/mL (LQC), 850 ng/mL (MQC), 9000 ng/mL (HQC), 10000 ng/mL (Back-up ULOQ) and 15000 ng/mL (ULOQ)
Minimum required dilutions (MRDs)	• 1:120 in Blocker Casein in PBS
Source and lot of reagents	• CT-P17: Celltrion, lot# CTP17CLN001 (RKAJ8), CTP17CLN002 (RKAJ8 and RKAJ9), CTP17CLN003 (RKAJ8 and RKAJ11), CTP17CLN004 (RKAJ8 and RKAJ9) • US-Humira®: AbbVie Ltd., lot# 1104991 (RKAJ8 and RKAJ9) • EU-Humira®: AbbVie Ltd., lot# 83349XH01 (RKAJ8 and RKAJ9) • Biotin-TNFα: (b) (4) (b) (4) • TNFα (for Sulfo-tagging): (b) (4) (RKAJ8, RKAJ9 and RKAJ11)
Regression model and weighting	• Four parameter logistic • $1/response^2$

Validation parameters	Method validation summary				Source location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	9			Table 2 of RKAJ8
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.20 to 1.93			Table 2 of RKAJ8
	Cumulative precision (%CV) from LLOQ to ULOQ	1.63 to 3.49			Table 2A of RKAJ8
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 5 QCs		CT-P17	US-Humira®	EU-Humira®	Table 3 of RKAJ8
		LLOQ	14.1	11.4	9.05	
		LQC	5.87	12.3	1.82	
		MQC	-1.32	4.40	5.68	
		HQC	5.48	7.92	-1.02	
		ULOQ	-2.13	3.04	-4.42	
	Inter-batch %CV		CT-P17	US-Humira®	EU-Humira®	Table 3 of RKAJ8
		LLOQ	21.5	14.9	16.6	
		LQC	7.30	6.44	10.8	
		MQC	7.38	5.45	8.45	
		HQC	5.86	4.23	5.29	
		ULOQ	7.17	5.66	4.82	
	Total Error (TE)		CT-P17	US-Humira®	EU-Humira®	Table 3 of RKAJ8
		LLOQ	35.5	26.3	25.7	
		LQC	13.2	18.7	12.6	
		MQC	8.70	9.84	14.1	
		HQC	11.3	12.2	6.32	
		ULOQ	9.30	8.71	9.24	

Selectivity & matrix effect	Blank matrix • 20 out of 20 unfortified healthy individual donors met the acceptance criteria • 19 out of 20 unfortified RA individual donors met the acceptance criteria CT-P17 • 10 out of 10 healthy individual donors fortified at the LLOQ level met the acceptance criteria • 10 out of 10 RA individual donors fortified at the LLOQ level met the acceptance criteria • 9 out of 10 healthy individual donors fortified at the HQC level met the acceptance criteria • 9 out of 10 RA individual donors fortified at the HQC level met the acceptance criteria US-Humira® • 10 out of 10 healthy individual donors fortified at the LLOQ level met the acceptance criteria. • 10 out of 10 RA individual donors fortified at the LLOQ level met the acceptance criteria. • 20 out of 20 healthy individual donors fortified at the HQC level met the acceptance criteria • 9 out of 10 RA individual donors fortified at the HQC level met the acceptance criteria EU-Humira® • 10 out of 10 healthy individual donors fortified at the LLOQ level met the acceptance criteria • 10 out of 10 RA individual donors fortified at the LLOQ level met the acceptance criteria • 10 out of 10 healthy individual donors fortified at the HQC level met the acceptance criteria • 9 out of 10 RA individual donors fortified at the HQC level met the acceptance criteria	Table 11 of RKAJ8
Interference & specificity	Concomitant Medication Interference • Methotrexate: No effect from 1.00 µg/mL methotrexate on the quantitation of CT-P17, US-Humira®, or EU-Humira®. • Folic Acid: No effect from 0.300 µg/mL folic acid on the quantitation of CT-P17, US-Humira®, or EU-Humira®. Target interference • No effect from 200 pg/mL TNFα on the quantitation of CT-P17, US-Humira®, or EU-Humira®.	Table 14, 15 of RKAJ8
Hemolysis effect	• No effect from hemolysis up to 5% fully lysed whole blood on the quantitation of CT-P17, US-Humira®, or EU-Humira®.	Table 12 of RKAJ8
Lipemic effect	• No effect from lipemia (> 300 mg/dL triglycerides) on the quantitation of CT-P17, US-Humira® or EU-Humira®.	Table 13 of RKAJ8

Dilution linearity & hook effect	Dilutional Linearity • 1000000 ng/mL CT-P17, US-Humira®, or EU-Humira® diluted 125-, 625-, and 3125-fold. • The accurate measurement of concentrations for the diluted samples was validated within the quantitative assay range. Hook Effect • No apparent hook effect observed at concentrations up to 1000000 ng/mL CT-P17, US-Humira®, or EU-Humira®.	Table 5, 6 of RKAJ8
Bench-top/process stability	Analyte Stability in Thawed Matrix (Bench-top) • 25 hours at room temperature for CT-P17, US-Humira®, or EU-Humira® Diluted Storage Analyte Stability • 24 hours at room temperature and 24 hours at 2 to 8 °C for CT-P17, US-Humira®, or EU-Humira®	Table 8, 10 of RKAJ8
Freeze-Thaw stability	• Six cycles thawed at room temperature for CT-P17, US-Humira®, or EU-Humira® • The freeze/thaw stability data met the criteria for all compounds for demonstrating stability.	Table 7 of RKAJ8
Long-term storage	• CT-P17: 364 days at -80 °C and 355 days at -25 °C • US-Humira®: 355 days at -80 °C and -25 °C • EU-Humira®: 355 days at -80 °C and -25 °C	Table 9 of RKAJ8, Table 8,9,10 of RKAJ9
Parallelism	• 14 out of 15 samples (93.3%) produced relative percent difference results ≤ 30%.	Table 5 of RKAJ11
Carry over	• N/A	N/A
Method performance in Study CT-P17 1.1		
Assay passing rate	• 98.1% (209/213)	Table 4 of RMMA
Standard curve performance	• Cumulative bias range: -1.85 to 3.55 (%DFT) excluding anchor point • Cumulative precision: 1.94 to 3.61 (%CV) excluding anchor point	Table 6 of RMMA
QC performance	• Cumulative bias range: -0.496 (LQC) / -2.69 (MQC) / 0.869 (HQC) (%DFT) • Cumulative precision: 6.63 (LQC) / 4.98 (MQC) / 4.94 (HQC) (%CV) • Total Error: 7.13 (LQC) / 7.67 (MQC) / 5.81 (HQC)	Table 7 of RMMA
Method reproducibility	• Overall % ISR Samples: 9.57% • Total % ISR Samples Pass: 99.5%	Table 8 of RMMA
Study sample analysis/ stability	• Samples were stored for a maximum of 132 days demonstrated long-term storage stability for CT-P17 in human serum at -80 °C.	RMMA
Standard calibration curve performance during accuracy and precision runs	Refer to 'Standard curve performance' above	
Method performance in Study CT-P17 1.3		
Assay passing rate	• 98.4% (123/125)	Table 4 of RMMR
Standard curve performance	• Cumulative bias range: -1.74 to 3.03 (%DFT) excluding anchor point • Cumulative precision: 1.62 to 3.00 (%CV) excluding anchor point	Table 6 of RMMR
QC performance	• Cumulative bias range: -1.15 (LQC) / -1.97 (MQC) / 1.58 (HQC) (%DFT) • Cumulative precision: 4.35 (LQC) / 2.94 (MQC) / 4.01 (HQC) (%CV) • Total Error: 5.50 (LQC) / 4.91 (MQC) / 5.59 (HQC)	Table 7 of RMMR
Method reproducibility	• Overall % ISR Samples: 10.3% • Total % ISR Samples Pass: 100%	Table 8 of RMMR
Study sample analysis/ stability	• Samples were stored for a maximum of 119 days demonstrated long-term storage stability for CT-P17 in human serum at -80 °C.	RMMR
Standard calibration curve performance during accuracy and precision runs	Refer to 'Standard curve performance' above	
Method performance in Study CT-P17 3.1		
Assay passing rate	• 95.0% (362/381)	Table 6 of RKMX2
Standard curve performance	• Cumulative bias range: -1.95 to 3.77 (%DFT) excluding anchor point • Cumulative precision: 1.55 to 3.06 (%CV) excluding anchor point	Table 8 of RKMX2
QC performance	• Cumulative bias range: 0.0225 (LQC) / -2.48 (MQC) / 1.54 (HQC) (%DFT) • Cumulative precision: 5.24 (LQC) / 4.08 (MQC) / 5.97 (HQC) (%CV) • Total Error : 5.26 (LQC) / 6.56 (MQC) / 7.51 (HQC)	Table 9 of RKMX2

Method reproducibility	• Overall % ISR Samples: 9.51% • Total % ISR Samples Pass: 95.6%	Table 10 of RKMX2
Study sample analysis/ stability	• Samples were stored for a maximum of 287 days demonstrated long-term storage stability for CT-P17 in human serum at -80 °C.	RKMX2
Standard calibration curve performance during accuracy and precision runs	Refer to 'Standard curve performance' above	

%CV: Percent coefficient of variation, %DFT: Percent difference from theoretical value, ECL: Electrochemiluminescent, HQC: High quality control, ISR: Incurred sample reanalysis, LLOQ: Lower Limit of Quantification, LQC: Low quality control, MQC: Mid quality control, MSD: Meso scale discovery, RA: Rheumatoid arthritis, TNFα: Tumor necrosis factor alpha, ULOQ: Upper Limit of Quantification

(source: Table 2.7.1-11 in 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods)

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