10 December 2020
EMA/47907/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Yuflyma

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/005188/0000

Note

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

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List of abbreviations

$\%AUC_{extrap}$	Extrapolated AUC percentage
%CV	Percent coefficient of variation
ACR	American College of Rheumatology
ACR20	ACR 20% improvement criteria
ACR50	ACR 50% improvement criteria
ACR70	ACR 70% improvement criteria
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
aDP	assembled Drug Product
AE	Adverse event
AESI	Adverse event of special interest
AHU	Air Handling Unit
AI	Auto-injector
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance model
AR	Assessment Report
AS	Ankylosing spondylitis
AST	Aspartate aminotransferase
AUC	Area under the (serum concentration-time) curve
AUC	Analytical Ultra Centrifugation
$AUC_{0\text{-}168hr}$	Area under the serum concentration-time curve from 0 to 168 hours
$AUC_{0\text{-}inf}$	AUC from time zero to infinity
$AUC_{0\text{-}last}$	AUC from time zero to time of last quantifiable concentration
AUT	Autoclave
BD	Becton, Dickinson
BLA	Biologic License Application
BLGF	Break Loose and Gliding Force
BLQ	Below the lower limit of quantification
BMI	Body mass index
BMWP	Biosimilar Medicinal Products Working Party
BPD	Biological Product Development
Brx	Bioreactor
CCM	Cell Culture Manufacturing
CD	Crohn's disease
CD	Circular Dichroism
CDAI	Clinical disease activity index
CDC	Complement-dependent cytotoxicity
CELISA	Cell-based enzyme-linked immunosorbent assay
CE-SDS	Capillary Electrophoresis-Sodium Dodecyl Sulfate

cGMP	current Good Manufacturing Practices
CHMP	Committee for Medicinal Products for Human use
CHO	Chinese Hamster Ovary
CI	Confidence interval(s)
cIEF	capillary Isoelectric Focusing
CIPC	Critical In-Process Control
CIPT	Critical In-Process Test
C1q	Complement component 1q / A subcomponent of complement C1, involved in immunoglobulin initiation of complement activation via the classical pathway
CL/F	Apparent total body clearance
CLL	Chronic Lymphocytic Leukaemia
C_{max}	Maximum serum concentration
CMC	Chemistry, manufacturing and control
COA	Certificate of Analysis
COP	Clean-Out of-Place
CPK	Creatine phosphokinase
CPP	Critical Process Parameters
CQA	Critical Quality Attributes
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CT-P17	Biosimilar adalimumab (CELLTRION)
C_{trough}	Trough serum concentration
CUP	Central Utilities Plant
CV	Coefficient of variation
CV	Column Volume
DAS28	Disease activity score 28 joints
DCS	Distributed Control System
DMARD	Disease modifying anti-rheumatic drug
DNA	Deoxyribonucleic Acid
DSC	Differential Scanning Calorimetry
DT	Doubling Time
ECG	Electrocardiogram
ECLA	Electrochemiluminescence assay
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency
EOS	End of study
EOW	Every other week
EPAR	European public assessment report
EPCB	End-of-Production Cell Bank
ESR	Erythrocyte sedimentation rate

EU	European Union
EULAR	European League Against Rheumatism
FACS	Fluorescence-Activated Cell Sorting
Fc	Fragment crystallizable region of immunoglobulin
FcRn	Neonatal Fc receptor
FcyR	Fc gamma receptor
FcyRI	Fc gamma receptor I
FcyRIIa	Fc gamma receptor IIa
FcyRIIb	Fc gamma receptor IIb
FcyRIIIa	Fc gamma receptor IIIa
FcyRIIIb	Fc gamma receptor IIIb
FDA	Food and Drug Administration
fDP	finished Drug Product
FTIR	Fourier Transform Infrared Spectroscopy
GBS	Guillain Barré syndrome
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
GVP	Good pharmacovigilance practices
GWD	Glassware Washer Drye
h	Hour(s)
HAQ	Health assessment questionnaire
HCCF	Harvested Cell Culture Fluid
HCP	Residual Host Cell Protein
HF	Human Factor
HPLC	High-Performance Liquid Chromatography
HRP	Horseradish Peroxidase
HS	Hidradenitis Suppurativa
HV	Healthy Volunteers
HVAC	Heating, Ventilation and Air Conditioning
IBD	Inflammatory Bowel Disease
ICH	International Council for Harmonisation
IEC-HPLC	Ion-Exchange High-Performance Liquid Chromatography
IFU	Instruction for use
IGF	Insulin like Growth Factor
IgG	Immunoglobulin G
IGRA	Interferon-γ Release Assay
IL-6	Interleukin-6
IND	Investigational New Drug
INN	International Non-proprietary Name
IPC	In-Process Control

IPM	In-Process Monitoring
IPT	In-Process Test
ISR	Injection site reaction
ITT	Intent-to-treat
IV	Intravenous
JIA	Juvenile idiopathic arthritis
K_D	Dissociation Constant
kDa	Kilodalton
LC-MS	Liquid Chromatography-Mass Spectrometry
LIVCA	*In vitro* Cell Age Limit
LOD	Limit of Detection
LOQ	Limit of Quantitation
LRV	Log Reduction Value
LS	Least square
LSM	Least squares mean
LTα3	Lymphotoxin-alpha3
MAA	Marketing Authorisation Application
MALS	Multi-Angle Light Scattering
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Micro-Flow Imaging
MLR	Mixed Lymphocyte Reaction
MoA	Mechanisms of Action
MOV	Maintenance Of Validation
MPA	Microscopic Polyangiitis
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSH	Material Storage and Handling
MTX	Methotrexate
NAb	Neutralizing antibody
NF	National Formulary
NHL	Non–Hodgkin's lymphoma
NSAID	Nonsteroidal anti-inflammatory drug
NWP	Normalised Water Permeability
OECD	Organization for Economic Cooperation and Development
ON	Optic neuritis
PASI	Psoriasis area severity index
PASI 75	Psoriasis area severity index score improvement of at least 75% relative to baseline
PBMC	Peripheral Blood Mononuclear Cell
PBS	Phosphate Buffered Saline
PC	Polycarbonate

PCA	Polymerase Cycling Assembly
pCD	Paediatric Crohn's disease
PD	Pharmacodynamic(s)
PFS	Pre-filled syringe
PFS-S	Pre-Filled Syringe with Safety guard (needle guard)
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PLC	Programmable Logic Controller
PML	Progressive multifocal leukoencephalopathy
PP	Process Parameter
PP	Per-protocol
PPD	Purified protein derivative
pPs	Paediatric Plaque Psoriasis
Ps	Plaque psoriasis
PsA	Psoriatic arthritis
PSUR	Periodic safety update report
PT	Preferred term
pUV	Paediatric Uveitis
PV	Process Validation
PVDF	Polyvinylidene Fluoride
QA	Quality Assurance
QC	Quality Control
Qp	Specific productivity
QS	Quantum satis
QTPP	Quality Target Product Profile
RA	Rheumatoid arthritis
RCB	Research Cell Bank
RH	Room Humidity
RMP	Risk management plan
RMP	Reference Medicinal Product
RNS	Rigid Needle Shield
RPLS	Reversible posterior leukoencephalopathy syndrome
SA	Scientific advice
SAE	Serious adverse event
SAWP	Scientific Advice Working Party
SC	Subcutaneous(ly)
SCC	Single Cell Clones
SD	Standard deviation
SDAI	Simplified disease activity index
SEC-HPLC	Size Exclusion High-Performance Liquid Chromatography
SF-36	36-item short form health survey

SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPR	Surface Plasmon Resonance
sTNFα	Soluble tumour necrosis factor alpha
T½	Terminal elimination half-life
TB	Tuberculosis
TEAE	Treatment emergent adverse event
TEM	Transmission Electron Microscopy
TESAE	Treatment-emergent serious adverse event
TFF	Tangential Flow Filtration
TK	Toxicokinetics
T_{max}	Time to C_{max}
tmTNFα	Transmembrane tumour necrosis factor alpha
TNFR	TNF receptor
TNFα	Tumour necrosis factor alpha
TOC	Total Organic Carbon
TSB	Tryptic Soy Broth
TSE	Transmitting animal Spongiform Encephalopathy
UC	Ulcerative colitis
uDP	unassembled Drug Product
UF	Ultrafiltration
UF/DF	Ultrafiltration/Diafiltration
US	United States
USP	United States Pharmacopoeia
USPI	US Product Information
UV	Uveitis
VAS	Visual analogue scale
WCB	Working Cell Bank
VCD	Viable Cell Density
VF	Viral Filtration
WFI	Water For Injection
Vss	Volume of distribution at steady state
V_z/F	Apparent volume of distribution during the terminal phase after non-intravenous administration
λ_z	Terminal elimination rate constant

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celltrion Healthcare Hungary Kft. submitted on 6 March 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Yuflyma, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indications:

Rheumatoid arthritis

Yuflyma in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Yuflyma can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Yuflyma in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Yuflyma can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1). Adalimumab has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Yuflyma is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1).

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Yuflyma is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Axial spondyloarthritis without radiographic evidence of AS

Yuflyma is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs).

Psoriatic arthritis

Yuflyma is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1) and to improve physical function.

Psoriasis

Yuflyma is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Paediatric plaque psoriasis

Yuflyma is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Hidradenitis suppurativa (HS)

Yuflyma is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy (see sections 5.1 and 5.2).

Crohn’s disease

Yuflyma is indicated for treatment of moderately to severely active Crohn’s disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's disease

Yuflyma is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

Yuflyma is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Uveitis

Yuflyma is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

Paediatric uveitis

Yuflyma is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

The legal basis for this application refers to:

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

The application submitted is

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

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Humira, 40mg, solution for injection
- Marketing authorisation holder: AbbVie Deutschland GmbH Co. KG
- Date of authorisation: 08-09-2003
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/03/256/001

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

- Product name, strength, pharmaceutical form: Humira, 40mg, solution for injection
- Marketing authorisation holder: AbbVie Deutschland GmbH Co. KG
- Date of authorisation: 08-09-2003
- Marketing authorisation granted by:
  - Union
- Marketing authorisation numbers: EU/1/03/256/001; EU/1/03/256/012-019; EU/1/03/256/023-25

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Humira, 40mg, solution for injection
- Marketing authorisation holder: AbbVie Deutschland GmbH Co. KG
- Date of authorisation: 08-09-2003; 28-07-2015; 28-07-2015
- Marketing authorisation granted by:
  - Union
  - Union Marketing authorisation numbers: EU/1/03/256/003; EU/1/03/256/013; EU/1/03/256/016

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
14/09/2017	EMEA/H/SA/3634/1/2017/III	Dr Peter Kiely, Prof. Brigitte Blöchl-Daum

The Scientific advice pertained to the following quality and clinical aspects:

- The adequacy of the proposed set of physicochemical and biological tests to demonstrate similarity to Humira in terms of quality;
- The overall design of the PK equivalence study, namely the study population and inclusion/exclusion criteria, dose and route of administration, endpoints, sampling time points and duration for PK and immunogenicity, sample size, choice of equivalence margin and the use of both EU-Humira and US-Humira in the study;
- The overall design of a phase III study conducted in plaque psoriasis patients, namely the study population and inclusion/exclusion criteria, dose, endpoints, the equivalence margin, the sample size and power, the time for the primary analysis, the blinding strategy and the use of US-Humira in the study;
- The size and scope of the proposed safety and immunogenicity database.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Melinda Sobor

The application was received by the EMA on	6 March 2020
The procedure started on	26 March 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	12 June 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	15 June 2020

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	17 June 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 July 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	11 September 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	N/A
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	12 November 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	17 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	25 November 2020
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Yuflyma on	10 December 2020

2. Scientific discussion

About the product

Yuflyma (company code: CT-P17) has been developed as a biosimilar to the reference medicinal product EU approved Humira.

Yuflyma is a genetically engineered recombinant human immunoglobulin IgG1 monoclonal antibody, which binds specifically to tumour necrosis factor alpha (TNF-α) and neutralises its biological function by inhibiting interaction with the p55 and p75 cell surface TNF receptors.

The proposed therapeutic indications for Yuflyma are identical to the indications in the EU approved Humira label: rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA; polyarticular JIA and enthesitis-related arthritis), axial spondyloarthritis (ankylosing spondylitis [AS] and axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis (PsA), psoriasis (Ps), paediatric Ps, hidradenitis suppurativa (HS), Crohn's disease (CD), paediatric CD, ulcerative colitis (UC), uveitis (UV) and paediatric UV.

Currently, Yuflyma is being developed and available only in 40 mg/0.4 mL (100 mg/mL) pre-filled syringe (PFS) and pre-filled pen (autoinjector (AI)) presentations. The recommended posology for adult and partial paediatric indications for Yuflyma are the same as for Humira. However, the originator is also available in vial and in 40mg/0.8mL, 80mg/0.8mL, 20mg/0.2mL strength. The vial size affects posology and in this respect, the proposed SmPC of Yuflyma is justifiably different from the originator regarding posology.

Type of Application and aspects on development

This Marketing Authorisation Application is an abridged application for a similar biological medicinal product under Article 10(4) of Directive 2001/83/EC as amended by Directive 2004/27/EC.

The development programme for Yuflyma was designed to demonstrate biosimilarity to the EU approved Humira.

The clinical development programme includes three clinical studies in healthy volunteers (HV) and two in RA patients (Studies CT-P17 1.1, 1.2 and 3.1 for biosimilarity; Studies CT-P17 1.3 and 3.2 for device development). The clinical development programme applied the following guidelines:

- Guideline on similar biological medicinal products (CHMP/437/04 Rev 1)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/ 42832/2005 Rev 1)
- Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010)
- Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**)
- Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004)
- Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1)

The applicant sought scientific and procedural advice from the CHMP (EMEA/H/SA/3634/1/2017/III) on the CT-P17 development programme, which covered questions on the quality, non-clinical and clinical program including a proposed Phase 3 study in patients with Ps. Overall, the development programme was compliant with CHMP guidance and scientific advice. However, after receiving final advice, the applicant revised the development plan. The proposed Phase 3 clinical study was revised to be conducted in patients with RA instead of Ps. Therefore, scientific advice was not given regarding study design and endpoints in the RA setting. Please also see section 1.1. "Scientific Advice".

The applicant has not submitted a paediatric investigation plan (PIP) for the current development programme, which is acceptable to CHMP, as this is a biosimilar medicinal product.

2.1. Quality aspects

2.1.1. Introduction

Yuflyma was developed as a biosmilar to Humira. The finished product is presented as a sterile solution for injection containing 40 mg of adalimumab as active substance.

Other ingredients are: acetic acid, sodium acetate trihydrate, glycine, polysorbate 80 and water for injections.

The product is available in 0.4 mL single dose pre-filled syringe (PFS), PFS with needle safety guard (PFS-S) or prefilled-pen (auto-injector, AI).

2.1.2. Active Substance

General information

The active substance, adalimumab (CT-P17) is a recombinant human monoclonal IgG1 antibody subclass antibody that selectively binds directly to human tumour necrosis factor α (TNFα).

Like other IgG subclasses, CT-P17 is a glycoprotein with one N-linked glycosylation site in the CH2 domain of each heavy chain. The molecular formulae for the heavy and light chains are $C_{2197}H_{3404}N_{584}O_{678}S_{15}$ and $C_{1027}H_{1610}N_{282}O_{332}S_{6}$ (considering C-terminal lysine cleavage: $C_{2191}H_{3392}N_{582}O_{677}S_{15}$ and $C_{1027}H_{1610}N_{282}O_{332}S_{6}$), respectively. Each heavy chain consists of 451 amino acids with 11 cysteine residues, and each light chain consists of 214 amino acids with 5 cysteine residues. The total mass of 145,189 Da is a theoretically predicted molecular mass intact CT-P17 molecule based on the amino acid sequence.

Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The manufacturing process is a straightforward monoclonal antibody production process. The active substance is produced in a Chinese Hamster Ovary CHO cell line. The manufacturing process starts with working cell bank (WCB) vial thaw and continues with inoculum expansion steps. The upstream process continues with seed bioreactor steps leading to production bioreactor. Cells are harvested via centrifugation and filtration, and finally transferred for purification.

Purification of CT-P17 is accomplished via three chromatography steps and finalised with ultrafiltration, virus filtration, and further filtration before filling into the sterile containers.

Detailed manufacturing flow charts for each process steps including non-critical and critical process parameters (input variables), and in-process tests (output variables) have been provided. In addition to manufacturing flow charts, descriptions of each process step have also been provided.

Control of materials

A standard, two-tiered cell banking system is in place. The description of the cell bank establishment is adequate and sufficient. Both master cell bank (MCB) and WCB are adequately tested for adventitious viruses. Additionally, specification for mycoplasma, sterility, and identity are in place. An acceptable protocol is presented for the preparation, qualification, and storage of future WCB. Limit of *in vitro* cell age has been evaluated and genetic stability demonstrated for cells of proposed age. Genetic stability studies have been performed and adequately demonstrated at end of production cells (EOPC) level. Genetic testing was performed also on the MCB. Program for monitoring the stability of the cell banks (WCB and MCB) has been provided. Stability will be monitored periodically. The method description and the summary of validation studies of the methods used to characterise and test the cell banks were provided.

Raw materials of biological and non-biological origin used for the manufacture of adalimumab CT-P17 are adequately presented. For the compendial materials reference is made to the Ph. Eur. and/or USP. For non-compendial raw materials, in-house acceptance criteria have been described. Upon request, information on growth media composition has been provided. In addition, a confirmation that an agreement is in place with the supplier of complex media to notify the applicant in case of changes to the medium has been provided. Raw materials of biological origin have appropriate specifications for identity and microbial safety.

Control of critical steps and intermediates

A comprehensive control strategy for CT-P17 active substance manufacture is in place. The development of the control strategy and, overall, the approach to define the criticality of parameters and in-process tests is in line with relevant EMA guidelines.

The presented process controls and in-process tests and for CT-P17 active substance manufacturing are appropriate. The applicant has presented target values and acceptable ranges for each process parameter and in-process test, which are, according to the applicant, based on development studies and/or historical production data. Historical data values for each parameter and a summary of process characterisation data used for establishing critical parameters and their acceptable ranges or acceptance criteria were provided.

Non-critical process parameters and tests are listed as part of the manufacturing flow charts and part of process validation studies.

Process validation

Process validation for CT-P17 active substance was carried out at commercial scale at the intended production site for CT-P17. Validation of the CT-P17 manufacturing process was performed at commercial scale using several batches. Process validation was performed by evaluation of the ability to control process parameters, ability to meet the acceptance criteria for all in-process tests, and the ability to meet specification for all routine tests. There was no batch failure during validation, and all active substance results met the acceptance criteria. Only few, minor deviations during process validation were identified, however all

the minor deviations were all adequately assessed and discussed. Based on the process validation data, it can be concluded that the process consistency was demonstrated by the input and output parameters and controls repeatedly meeting their requirements.

Several hold points during active substance manufacturing process were identified. Maximum hold times for each hold points were appropriately validated. In addition, validated hold times for buffers and cell culture media were adequately established. Resin lifetime studies were performed in small-scale models. Establishment and qualification of small-scale models was performed and adequately described. Maximum hold time of thawed active substance has been defined.

The capability of the purification process to reduce process-related impurities was sufficiently demonstrated by small-scale impurity clearance studies. Methods have been adequately described. Data for small-scale qualifications have been provided and considered acceptable. The impurity clearance validation studies are further supported by the low impurity levels measured in CT-P17 active substance as well as process validation data of commercial scale batches confirming the removal of impurities to acceptable levels.

Reprocessing of virus filtration, ultrafiltration/diafiltration (UF/DF) pool and final filtration have been studied in small-scale but are not yet validated in commercial manufacturing scale. Reprocessing will be validated if need for such occurs. Based on a small-scale data, acceptance criteria for reprocessing at manufacturing scale has been set. The approach is considered acceptable.

All liquid filters used for media preparation, bioreactors, harvest, purification, buffer preparation and hold are part of the validation studies. The filters were categorised based on risk assessment to designate the required tests for filter validation studies. Results of the filter validation studies were provided and are considered acceptable.

The shipping container is maintained at the recommended storage conditions during transportation. The presented shipping validation studies cover the shipping of CT-P17 in the active substance container representing the worst-case scenarios. Summary data from the shipping validation was provided confirming that all the tested quality attributes met the acceptance criteria.

Manufacturing process development

Four different processes (A to D) have been described for CT-P17 active substance. Non-clinical studies were performed using material from Process A and B batches, Process C material was used for clinical studies and Process D material was used for process validation and similarity studies. Process D is the proposed commercial process.

Comparability between Process A and B, Process B and C, as well as Process C and D was appropriately demonstrated. The comparability assessment between Process C and Process D is discussed below in more detail.

For Process D upstream process, only minor changes were introduced to when compared to Process C manufacture. For the downstream process, a number of adaptations were made. Comparability study included several batches of Process C and several batches of Process D, which were, with some exceptions, compared side-by-side by using batch release tests as well as other physicochemical/biological tests. Furthermore, additional evaluation was performed for in-process tests for several batches from each process. No significant differences in quality attributes were observed. Stability profile on each process batches was also studied demonstrating similar stability.

In conclusion, based on the comparability data, the quality and physicochemical and biological characteristics of the Process C active substance used in clinical studies and commercial Process D active substance material are considered comparable.

Characterisation

A summary of the characterisation studies has been provided. The studies are further discussed in the Biosimilarity section. The characterisation of CT-P17 adalimumab included determination of structure (primary, secondary, and higher-order), charge variants, N-linked glycans, disulphide bonds, free thiols, and thermal stability. In general, the studies included in the characterisation are considered comprehensive and relevant.

All process-related impurities were observed in constant low levels and the presented data demonstrate that the CT-P17 active substance manufacturing process for commercial production clears process-related impurities to acceptable levels. The approach to control process-related impurities can be supported. Summary tables including safety evaluation of each impurity have also been provided.

Specification

Specification

The release specification proposed for the active substance includes tests for appearance, identity, purity/impurity, quantity, potency attributes, endotoxins and bioburden. All the specifications were set in accordance with guideline ICHQ6B.

The proposed active substance specification includes compendial tests (clarity, colour, pH, endotoxin, and bioburden) and non-compendial tests (identity, oligosaccharide profile, purity, charge variants, process related impurities, protein concentration, and potency by *In vitro* hTNFα Neutralisation.

The biological activity of CT-P17 finished product is determined based on the human Tumour Necrosis Factor-α (hTNFα) neutralisation assay.

Overall, the test parameters proposed to be included in the active substance specification are considered relevant and in line with the current guidance. The applicant has also discussed all the test acceptance criteria separately. Justification as well historical data for each acceptance criteria have been provided. Generally, the approach to set the acceptance criteria solely on statistical evaluation is not fully supported, as the acceptance criteria for release and stability should be set based on manufacturing history including clinical qualified batch data and characterisation data from the reference medicinal product. However, in this particular case, very little variation between batches is observed and thus, the proposed limits are tight enough and supported by the clinical batch data.

Acceptance criteria for total level of the main fucosylated species, G0F, G1F and G2F is proposed to be controlled. In addition, major afucosylated species and high mannose variants are controlled. Additionally, upon request, the applicant proposed to set a new specification for total afucosylated glycans %, which is considered appropriate. As proposed to control the most important glycan species is considered acceptable.

Based on the provided batch analysis data, these approaches are considered acceptable.

Analytical methods

A summary of the analytical methods validation has been provided. Analytical results of several batches have been submitted, manufactured by Process A, Process B, Process C and Process D. All results are within specification of the corresponding stage of development.

The validation verification results for compendial methods have been presented in the dossier. For non-compendial methods, validation reports were also provided and based on the provided data the methods are considered appropriately validated for their intended use.

In conclusion, the applicant has followed the principles of ICH Q2R1 guideline to demonstrate the validity of the methods.

Batch analysis

Batch analysis data from CT-P17 active substance several lots used in the non-clinical studies, clinical studies, and stability studies have been provided. Batch data from all manufacturing processes A to D have also been provided. All acceptance criteria were met.

Reference standard

The strategies for establishing the reference standards (RS) during the active substance development have been provided. The reference standards used throughout the product development have been adequately described. The applicant has a plan to establish a two-tiered system for in-house reference material involving primary and working reference standards. The characterisation tests and analytical procedures for establishing a new working reference standard (WRS) were provided.

In conclusion, the reference standards have been adequately presented and thoroughly qualified.

Container closure system

The active substance containers are pre-sterilised (by gamma irradiation), pyrogen free bottles. Containers are stated to meet pharmacopoeial requirements. Specifications for containers are in place including description, cytotoxicity, endotoxin, and gamma irradiation. Certificates of Analysis (CoAs) from the supplier as well as representative drawings of the containers have been provided. Gamma irradiation is performed by the supplier. Non-compendial container closure integrity test was performed to study the suitability of the containers for its intended use. Adequate information about compliance of the containers with Ph. Eur. has been provided.

Summary data from extractable and leachable studies of primary containers of active substance have been provided. Furthermore, a risk assessment for disposable materials used for manufacture has also been provided. Based on the provided data it can be concluded that low levels of leachables are present in the active substance and they are not expected to pose a safety risk.

Stability

Stability data has been provided on several active substance batches at long term, intermediate, accelerated and stressed storage conditions. In addition, a photo stability study has been performed confirming that the active substance is photo-sensitive. Stability studies were carried out according to the Guideline ICHQ5C. All stability samples have been stored in model containers of the same material as the actual active substance container. The model containers have been filled to represent the worst-case surface area to volume ratio at scale of active substance containers. The use of reduced size containers representative of the commercial

scale containers in the stability studies is acceptable. Real-time data is currently available for several batches representative of clinical material and commercial active substance. No critical changes or significant trends have been observed in the tested parameters at the long-term conditions or in the completed intermediate storage condition study. The applicant commits to continue testing all of the CT-P17 active substance batches included in the stability studies. In the event that stability test results are not within the limits of the specification at any time point, the regulatory authorities will be informed.

Overall, the stability of the active substance has been adequately addressed. As stated in ICH Q5C guideline, primary data to support a requested storage period should be based on long-term, real-time, real-condition stability studies. Thus, the claimed shelf life for the active substance when stored at the recommended storage conditions is considered acceptable.

2.1.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Description of the product

The finished product is formulated for subcutaneous (SC) administration as a sterile solution in a pre-filled syringe (PFS), PFS with needle safety guard (PFS-S) or pre-filled pen (auto-injector, AI) intended to deliver 40 mg of adalimumab per 0.4 mL solution at a concentration of 100 mg/mL. Besides the active substance, adalimumab, the finished product solution also contains acetic acid, sodium acetate trihydrate, glycine, polysorbate 80 and water for injections.

Pharmaceutical development

The Quality Target Product Profile (QTPP) profile was developed in accordance with ICH Q8 (R2): Pharmaceutical development, taking into consideration the intended use in clinical setting, route of administration, dosage form, physical, chemical, biological or microbiological properties, dosage strength, container closure system, sterility, purity, and stability.

Formulation development

The optimal stabiliser was evaluated in two formulation studies. In the first study, formulations with various stabilisers (e.g, sugars and amino acids) were compared after storage at long-term condition (5 ± 3°C), at accelerated condition (40 ± 2°C / 75 ± 5% RH), and after freeze/thaw stress. Formulation with optimal concentration of glycine was chose as the final stabiliser. The formulation studies demonstrated that the optimal formulation for Yuflyma contains glycine, sodium acetate, polysorbate 80 and protein concentration of 100 mg/mL.

Manufacturing process development

Several changes to the finished product manufacturing process were implemented during the manufacturing process development. The product formulation, manufacturing site and scale were changed. In addition, minor changes and adjustments to some of the analytical methods were included due to manufacturing site and equipment changes.

Several manufacturing processes were described for the finished product. Processes were used for non-clinical studies, comparability studies, clinical studies and process validation. The process used for process validation is the proposed commercial manufacturing process.

Extensive comparability studies were conducted between consecutive processes and demonstrated that the consecutive manufacturing processes are comparable. Comparability between the commercial process and the process used in clinical studies was shown using additional physicochemical and biological characterisation studies and all results were similar.

Container closure

The safety and effectiveness of the auto-injector has been assessed in usability studies with the intended users and in its intended environment. The usability studies have been assessed in detail in the clinical assessment report.

The medical devices have been appropriately studied for suitability for use, functional performance, container closure integrity, usability study, mechanism of action.

Microbiological attributes

The microbial safety of the active substance, excipients and finished product is effectively controlled. The container closure components are sterilised, and the integrity of container closure system was confirmed.

Manufacture of the product and process controls

Manufacturers

The information given on the finished product manufacturers is found acceptable.

Manufacturing process

The finished product manufacturing process consists of formulation, sterile filtration, aseptic filling and visual inspection processes, to produce the finished product as an unassembled finished product (uFP) in a pre-filled syringe without plunger rod. The uFP is further assembled into prefilled syringes (PFS), pre-filled syringes with safety guard (PFS-S) or auto-injector (AI). The manufacturing process was described in sufficient detail.

Control of critical steps and intermediates

The manufacturing process is controlled by raw material testing and several process variables that have defined target set-points/operating ranges and/or defined acceptance limits.

Characterisation of active substance and finished product batches demonstrated that the finished product manufacturing process has no impact on aggregation, fragmentation, charge variants, glycosylation or potency.

The process control strategy for the finished product manufacture is acceptable. In-process controls (IPCs) (with acceptance criteria) and critical process parameters (CPPs) are defined for each process step where relevant. Overall, the IPC tests and proposed limits are considered acceptable. Critical quality attributes (CQAs) were determined based on knowledge from previous commercial manufacturing experience as well as characterisation and similarity assessment with the reference product Humira. Comprehensive lists of CPPs and critical in-process controls linked to relevant CQAs were provided.

Manufacturing process validation

The manufacturing process steps were validated using several validation batches of uFP. Manufacturing process validation data for formulation of final bulk, sterile filtration, aseptic filling, visual inspection, and assembly of the final finished product were provided. Process validation data included process parameters, in-process controls and release specification testing. All process validation results were within acceptance limits. The sterilisation processes of equipment and container closure components were qualified.

Product specification

The specification for routine release of finished product includes compendial tests for clarity, colour, visible particles, pH, extractable volume, osmolality, uniformity of dose, sub-visible particles, endotoxin, and sterility.

Non-compendial tests for identity, purity, concentration, and potency are in place. Furthermore, functionality tests for PFS and PFS-S are presented. A comprehensive panel of specifications has been presented for the finished product release and shelf-life specification.

Acceptance limits for individual test parameter were generated. Similar specification limits have been set as for the active substance. For shelf life acceptance criteria slightly wider acceptance criteria is proposed for charge variants. This is considered acceptable and justified by the stability data.

Characterisation of impurities

No additional impurities are detected in the CT-P17 finished product compared to the active substance. For discussion on impurities please refer to the Characterisation section.

A summary of the risk assessment for elemental impurities in accordance with ICH Q3D has been provided. Furthermore, the presence of possible nitrosamine impurities was discussed, and a risk assessment was provided. Based on the provided assessments, the risk for elemental and nitrosamine impurities in the CT-P17 finished product is considered negligible.

Analytical methods

Similar methods with few exceptions are used for CT-P17 finished product. Release tests used specifically for the finished product are functionality tests for the uFP, PFS, PFS-S and AI.

Batch data

Batch analysis data derived from several lots of CT-P17 finished product manufactured throughout development are presented. These lots are manufactured using manufacturing process used for non-clinical, clinical, and stability as well as biosimilarity studies. All lots met the acceptance criteria in place at the time of release.

Container closure system

The finished product is presented as a solution for injection in a pre-filled syringe with a plunger stopper and a needle with a needle shield.

The primary packaging components that comes into direct contact with the finished product are: the borosilicate glass syringe with a pre-staked needle (unassembled FP, uFP) and an elastomeric plunger stopper. Overall, the description of the primary and secondary container closure system as well as safety and usability of the devices are deemed sufficient and acceptable from the quality point of view.

Stability of the product

Data have been provided on finished product stability studies performed at the long-term storage condition, at the accelerated storage condition, and at the stress storage condition. Stability studies have been conducted on 2 presentations: uFP (unassembled FP i.e. CTP17 FP in a PFS) and AI (uFP assembled with syringe unit and drive unit). The finger flange, plunger rod, and safety guard are assembled on top of the PFS and are not in direct contact with the CT-P17 FP solution, and thus are likely to have no impact on the stability of the CT-P17 FP solution. It is agreed that the stability data from CT-P17 uFP represent also stability of the assembled CT-P17 PFS and CT-P17 Pre-Filled Syringe with Safety guard (needle guard) (PFS-S).

Real-time data is available for several uFP lots. There were no significant changes in the quality attributes of CT-P17 finished product during storage at the long-term conditions during the submitted period. In functionality stability testing of CT-P17 finished product devices, CT-P17 uFP met the acceptance criteria for break loose and glide forces following storage during the submitted period under long-term storage conditions. For the CT-P17 AI, all functionality stability test results met the acceptance criteria following storage during the submitted period under long-term storage conditions.

Overall, the stability of Yuflyma finished product has been adequately addressed. As stated in ICH Q5C guideline, primary data to support a requested storage period should be based on long-term, real-time, real-condition stability studies. Thus, the proposed shelf-life of 2 years when stored at 2°C – 8°C is acceptable.

The proposed additional shelf-life claim of 30 days for CT-P17 finished product when stored at 25±2°C is supported by the provided data and acceptable.

A confirmatory photostability study was performed and the results of the study indicated that CT-P17 finished product (uFP) secondary packaging provides sufficient protection from light as Yuflyma is photostable when stored in its carton package or in the assembled AI.

In conclusion and based on the stability data provided the proposed shelf-life of 2 years when stored at 2°C – 8°C is acceptable for the finished product. Yuflyma may be stored at temperatures up to a maximum of 25°C for a period of up to 30 days. The pre-filled syringe or pre-filled pen must be protected from light and discarded if not used within the 30-day period.

Biosimilarity

The finished product was formulated as a biosimilar to Humira. However, there are some minor differences in the compositions of Yuflyma and Humira: the formulation of Yuflyma is different from Humira.

Similarity assessment

A comprehensive similarity exercise following the general principles outlined in the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance - Quality issues (EMA/CHMP/BWP/247713/2012) has been performed (Table 1). The comparability studies have been done by analysing Yuflyma and Humira-EU, side-by-side with qualified state-of-the-art physicochemical and biological methods. Active substance batches included were independent of active substance batches used to produce finished product batches included in the similarity assessment. The batches reflected a range of expiration dates and product ages.

The quality range was set by statistical analysis of several batches of Humira-EU for key biological assays related to the known and putative mechanisms of action of adalimumab. Overall strategy was included, when differences were observed, to evaluate the potential of these on safety, efficacy, PK/PD and immunogenicity.

Method qualification

Extensive orthogonal methodologies applied to CT-P17 and Humira-EU for similarity assessment were qualified where feasible, performance parameters i.e. precision, specificity and/or accuracy was applied on a case by case basis, using the principles of method validation as defined in ICH Q2 (R1). A summary of qualification results for physicochemical test methods was presented. Upon request the applicant provided the qualification/validation reports to demonstrate that the methods used in biosimilarity characterisation are suitable for the intended use.

Summary of results

An overall Summary and results of a 2-way similarity assessment is presented in the table below.

Table 1 Overall Summary of 2-way Similarity Assessment

Similarity Attributes	Analytical Test Method	Summary of Results	Conclusions
Primary Structure	N-terminal Sequencing C-terminal Sequencing Peptide Mapping (LC-MS) Intact Mass (LC-MS) Glycation	EU-approved Humira® and CT-P17 have identical primary structure. Minor differences between the two products were detected in levels of N-terminal pyroglutamic acid, oxidation, C-terminal lysines, proline amidation and glycation of the light chain. Other post-translational modifications were observed to be at similar levels.	A slight difference in the amount of N-terminal pyro-glutamate and C-terminal lysine variants is not considered clinically relevant. The difference in oxidation is small and considered not clinically significant) and a forced degradation study showed that a substantial increase in oxidation has no impact on TNFα neutralisation activity, CDC activity, or FcγRIIIa binding affinity. IEC-HPLC peak fractionation studies suggest that proline amidation has no adverse effect on FcγRIIIa-V binding affinity, FcRn binding affinity, TNFα neutralisation activity or CDC activity. A lower level of glycation is generally considered a desirable quality characteristic and none of glycation sites exists in either epitope or Fc receptor binding regions. Therefore, the small differences in levels of post-translational modifications are not considered to be clinically meaningful.
Higher order Structure	Free Thiol Analysis Disulphide Bonds FTIR DSC CD	CT-P17 has identical disulphide bond structure to EU-approved Humira®. The free thiol levels of CT-P17 were slightly higher than EU-approved Humira®. CT-P17 was highly similar in secondary and higher order structure.	Considering other high order structure analysis results which showed high similarity between the products, the small difference in free thiols does not appear to affect antibody structure or biological activities.

Similarity Attributes	Analytical Test Method	Summary of Results	Conclusions
Content	Protein Concentration Extractable Volume	CT-P17 and EU-approved Humira® had similar protein concentrations. The extractable volume of the two products was highly similar and both products had a mean extractable volume of 0.41 mL.	The data for protein concentration and extractable volume show that CT-P17 and EU-approved Humira® deliver the same dose of adalimumab.
Aggregates and Monomeric Purity	SEC-HPLC SEC-MALS AUC MFI	CT-P17 and EU-approved Humira® predominantly contain monomer with low levels of HMW and very low levels of LMW. CT-P17 had a slightly higher level of HMW than EU-approved Humira by SEC-HPLC and AUC. CT-P17 and EU-approved Humira® are comprised of a single dominant monomer species (95.2 – 98.3% in abundance) with an S-value of 6.7 The numbers of sub-visible particles in CT-P17 determined by MFI were comparable to, or lower than, those of EU-approved Humira® batches.	Levels of HMW remained < 1%, and had no impact on biological activities and no impact on immunogenicity or safety in clinical studies. Therefore, the slightly higher level of HMW in CT-P17 has no significant effect on safety and efficacy.
Fragmentation Aglycosylation	CE-SDS (Reduced and Non-reduced)	CE-SDS analysis showed that CT-P17 has a slightly lower level of non-glycosylated heavy chain and a lower level of fragments than EU-approved Humira®.	Lower levels of these impurities are generally considered to be desirable and had no effect on biological activities.
Charged Variants	cIEF IEC-HPLC	The same five major peaks (Peak 1-5) and three minor peaks (Peak 1a, Peak 4a and Peak 5a) were detected by cIEF in both CT-P17 and EU-approved Humira®, and the pI of each peak was the same in the two products IEC-HPLC suggested that CT-P17 and EU-approved Humira® contain the same or similar charge variants. Some minor differences were noted in the relative proportion of the 6 IEC-HPLC peaks/peak groups. CT-P17 had lower levels of acidic group and basic group 1 and higher levels of main peak. CT-P17 also had a slightly higher level of basic group 2 than EU-approved Humira®.	The lower level of the acidic group and basic group 1, and higher level of main peak as observed in CT-P17 are generally considered desirable in a mAb. Although CT-P17 contains 0.6% higher level of basic group 2 containing CT-P17 specific form than EU-approved Humira®, it is so small as to be highly unlikely to have an adverse impact on the efficacy and safety of CT-P17, as is supported by data on biological activities and by the clinical study data.
Glycosylation	Oligosaccharide profile N-linked glycan analysis	The types and proportions of the glycans were reasonably conserved between EU-approved Humira® and CT-	Small difference in high mannose content is not expected to impact PK in humans in a measurable manner. Since the levels of total afucosylated

Similarity Attributes	Analytical Test Method	Summary of Results	Conclusions
		P17. CT-P17 had lower levels of mannosylated glycans and higher levels of afucosylated glycans. Statistical analysis showed that over 90% of CT-P17 samples were within the quality range of EU-approved Humira® in total afucosylated glycans.	glycans (mannosylated glycans + afucosylated glycans) in CT-P17 were similar to EU-approved Humira® and biological activities including FcγRIIIa-V and ADCC are highly similar, CT-P17 can be considered to be similar to EU-approved Humira® in glycosylation profile and minor differences in levels of individual glycan species are highly unlikely to be clinically meaningful
Biological activity (F(ab')2-related Function)	*In vitro* TNFα neutralisation TNFα biding affinity tmTNF binding affinity Apoptosis (reverse signaling)	CT-P17 was highly similar to EU-approved Humira® in binding to TNFα and neutralisation of TNFα which are the primary mechanism of action of adalimumab. CT-P17 was also highly similar to EU-approved Humira® in binding to tmTNFα and in apoptosis induced by reverse signalling following binding to tmTNFα	There is no residual uncertainty related to biological activities. CT-P17 and EU-approved Humira can be expected to have similar efficacy *in vivo*.
Biological Activity (Fc-related Binding)	C1q binding FcγRIIIa-V binding affinity FcγRIIIa-F binding affinity FcγRIIIb binding affinity FcγRIIa binding affinity FcγRIIb binding affinity FcγRI binding affinity FcRn binding affinity	CT-P17 was highly similar to EU-approved Humira® in activities relevant to putative mechanisms of action of adalimumab, including C1q binding affinity, FcγRIIIa-V binding affinity, FcγRIIIa-F binding affinity, FcγRIIIb binding affinity, FcγRIIa binding affinity, FcγRIIb binding affinity, FcγRI binding affinity, and FcRn	There is no residual uncertainty related to biological activities. The high similarity in Fc-receptor binding affinity and C1q binding support that the products can be expected to have the same Fc-receptor mediated effects *in vivo*. The high similarity in FcRn binding affinity suggests that the products can be expected to have the same PK profile *in vivo*.
Fc-Related Biological Activities (Fc-F(ab')2-related Function)	CDC ADCC	CT-P17 drug product and EU-approved Humira® showed similar biological activities in the additional biological properties relevant to inflammatory bowel disease.	There is no residual uncertainty related to biological activities relevant to IBD. CT-P17 can be expected to mediate the same effects as EU-approved Humira® in IBD.
Additional Biological Properties Relevant to IBD Indications and LTα3 Binding	TNFα-induced apoptosis inhibition assay TNFα-induced IL-8 release inhibition assay TNFα-induced VCAM-1 release inhibition assay Induction of regulatory macrophages in MLR assay Inhibition of cellular proliferation in MLR assay $LT\alpha_3$ binding assay (ELISA)	CT-P17 drug product and EU-approved Humira® showed similar biological activities in the additional biological properties relevant to inflammatory bowel disease (IBD).	There is no residual uncertainty related to additional biological activities relevant to IBD. CT-P17 can be expected to mediate the same effects as EU-approved Humira® in IBD. Neither CT-P17 or EU-approved Humira bind to $LT\alpha_3$.

Similarity has been demonstrated for physico-chemical and biological quality attributes. The observed differences were small and unlikely to have a clinical impact. Minor differences noted were mainly in charge variants, in mannosylated and afucosylated glycans.

N-terminal cleaved form at heavy chain was exclusively detected in CT-P17 basic group 2 region by IEC-HPLC, but in small quantities. Upon request, the applicant provided further discussion on the potential impact of N-terminal cleaved form variant on functional properties and safety. According to the applicant, the cleaved form is considered as a product-related impurity, which can be controlled by IEC-HPLC at in process as well as active substance and finished product specification levels. It was emphasised, that the cleaved form was a biosynthetic variant, which is mostly removed during the downstream purification process, it is not a degradation product, and therefore it can be effectively controlled. Data from long-term, accelerated and stress stability studies did not reveal any sizeable increase in % area basic group 2, therefore accumulation of the cleaved form during storage is not expected. Furthermore, the low amount of the variant (≤ 2% basic group 2) is unlikely to have an impact on the functional properties of the CT-P17 active substance. This conclusion can be agreed upon.

High mannose species were slightly higher in EU-approved Humira and afucosylated species were slightly lower in EU-approved Humira in comparison to CT-P17, but the total afucosylated glycans (Sum of high mannose species and afucosylated species) were similar between EU-approved Humira and CT-P17. The differences observed in the glycans did not result in a detectable difference in Fc related biological activity and are unlikely to have any clinical impact. Upon request, the applicant has included a new active substance release specification for total number of afucosylated species.

In accelerated and stressed conditions, the stability profiles of CT-P17 and EU-approved Humira were similar. In the forced degradation studies under oxidative stress, UV stress, high temperature stress, and high pH stress conditions, the data further support the similarity of CT-P17 finished product, and EU-approved Humira. Different degradation profiles of CT-P17 FP and EU-approved Humira were observed under low pH (acidic stress), which is anticipated as the result of the different formulation composition.

In conclusion a high similarity between CT-P17 and Humira-EU has been demonstrated for the following physico-chemical and biological properties:

- Primary and higher order structure
- Content and extractable volume
- Size heterogeneity
- Charge variants (with some minor exceptions)
- Glycan profiles
- Binding to soluble and transmembrane TNFα and neutralisation of TNFα
- Reverse signaling activity
- Binding to Fc-receptors (FcγRIIIa [V, F], FcγRIIIb, FcγRIIa, FcγRIIb, FcγRI and FcRn)
- Binding to C1q and CDC activity
- ADCC activity
- Inhibition of TNFα-induced apoptosis, IL-8 and VCAM-1 release
- Induction of regulatory macrophages and subsequent T-cell anti-proliferation
- Stability under accelerated and stressed conditions and forced degradation

Adventitious agents

The manufacturing process of Yuflyma does not contain raw materials of human origin, however, some materials of animal origin are included.

A TSE certificate for a raw material has been provided. Risk of TSE contamination of each animal origin material has been evaluated and the risk is considered negligible. Cell banks are appropriately tested free of adventitious viruses indicating that these animal-based materials are an unlikely source of viral contamination.

For the risk of mycoplasma, fungal and microbial contamination adequate data have been provided. Sufficient microbial control is in place. The cell banks are sterile and tested unprocessed bulk batches have very low bioburden. In addition, bioburden is controlled throughout the manufacturing process.

Yuflyma is expressed in the well-described Chinese Hamster Ovary (CHO) cells, which are known to express retrovirus-like particles (RVLPs). The applicant determined the retroviral burden from cell culture supernatants of three different Process D batches. Methods used for viral testing of unprocessed bulk are listed in the dossier. Adequate validation reports have been provided.

Viral clearance studies are performed. Four model viruses were chosen for viral clearance studies. The methods used for viral titer testing has been described. Summary data from viral clearance studies performed in small-scale columns has been provided. Comparison of process parameters used in virus clearance study and production scale as well as and the rationale for parameters has been appropriately described.

The purification processes steps involved in viral removal include two chromatography steps, virus inactivation and virus filtration. The applicant has also provided adequate viral clearance study data from used resins. The assays used for viral testing have been described. Overall, it can be concluded from the summary table and provided validation report that the viral clearance and inactivation studies performed result in a satisfactory outcome.

Only endogenous retrovirus particles have been observed in the MCB and EPCB by transmission electron microscopy (TEM) examination. The manufacturing process has been validated and provides assurance that endogenous particles are sufficiently removed during purification processes.

GMO

Not applicable.

2.1.4. Discussion on chemical, pharmaceutical and biological aspects

In general, the provided Module 3 for Yuflyma is of good quality and relevant areas have been satisfactorily covered.

Overall, the manufacturing process of the active substance and finished product and the control strategy have been appropriately presented.

The similarity between Yuflyma and the reference product, Humira-EU has been addressed in a comprehensive comparability exercise. Based on the provided quality data similarity between Yuflyma and Humira-EU can be agreed upon.

2.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Yuflyma is considered acceptable when used in accordance with the conditions as defined in the SmPC.

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance is adequately described, controlled and validated. The active substance is well characterised and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents' safety including TSE have been sufficiently assured.

2.1.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended a point for further investigation.

2.2. Non-clinical aspects

2.2.1. Pharmacology

The pharmacological activity of CT-P17 and Humira-EU was characterised in a series of comparative *in vitro* studies in a stepwise manner. The biological assays evaluated Fab-related biological activity of adalimumab as it engages with its target TNFα and the Fc-based functionality that can affect the effector functions and pharmacokinetics.

Two-way *in vitro* similarity assays with CT-P17 100 mg/mL and Humira-EU 100 mg/mL were included as part of the Quality dossier (see Section 2.1.).

Sufficient number of batches of CT-P17 and Humira-EU were included in the similarity exercise . The similarity analyses were performed side-by-side using qualified in-house reference standard.

CT-P17 was similar to Humira-EU in binding to TNFα and tmTNFα, C1q and Fc receptors (FcγRIIIa [V type and F type], FcγRIIIb, FcγRIIa, FcγRIIb, FcγRI and FcRn) and in TNFα neutralisation, CDC, ADCC and apoptotic activity (reverse signalling). The glycan profiles were similar with some minor variation in the high mannose and afucosylation contents. CT-P17 had slightly higher total afucosylation contents being 8.08 % ± 0.7 than Humira-EU (6.80 % ± 0.6), but this difference did not result in differences in the Fc-related functions, i.e. binding to FcγRIIIa and ADCC activity.

The additional biological assays which were done to support the extrapolation to other indications (including inflammatory bowel disease), indicated that CT-P17 and Humira-EU had similar effects on inhibition of TNFα-induced apoptosis, IL-8 and VCAM-1 release, regulatory macrophage induction and subsequent T-cell anti-proliferation.

2.2.2. Pharmacokinetics

No separate pharmacokinetic studies were conducted to support biosimilarity of CT-P17 and Humira-EU.

One toxicology/toxicokinetic study with CT-P17 and Humira-EU was conducted in cynomolgus monkeys for support of the similarity assessment (see section 2.2.3. Toxicology). Validated electrochemiluminescence assays were used for measurement of CT-P17 and Humira-EU and anti-CT-P17 or anti-EU-approved Humira antibodies in monkey serum. The data did not allow drawing of definite conclusions of serum concentration-time profile similarity of CT-P17 and Humira-EU due to the study limitations (see section 2.2.5. Discussion on nonclinical aspects).

2.2.3. Toxicology

Repeat dose toxicity

A 28-day repeat-dose toxicity study (with TK and immunogenicity testing) in cynomolgus monkeys was conducted to support the safety of CT-P17 and to detect any biologically relevant differences between CT-P17 and the reference product Humira-EU to support clinical trials in patients, and to meet the requirements for a global development strategy.

Analytical bridging studies demonstrated that an early pilot scale finished product process 1 CT-P17 finished product used in the toxicology study was comparable with CT-P17 scaled up commercial manufacturing process finished product, used in analytical and functional similarity studies and clinical trials.

Once weekly subcutaneous administration of 32 or 157 mg/kg CT-P17 and Humira-EU was well tolerated. The only CT-P17- or Humira-EU related observations were microscopic findings in the immune system in lymph nodes, spleens, or thymus, and were as expected, and in line with the findings reported in cynomolgus monkeys with same Humira doses in the registration studies. Microscopic changes at the injection site occurred with a low incidence and minimal severity and were similar in CT-P17 and Humira-EU treated animals.

The mean concentration-time profiles for CT-P17 or Humira-EU increased with the increase in dose level from 32 to 157 mg/kg. The increases in mean maximum serum concentration (C_{max}) and $AUC_{0-168hr}$ values were generally dose proportional. There were no consistent differences between males and females in individual serum concentration-time profiles, $AUC_{0-168hr}$ (female to male $AUC_{0-168hr}$ ratios ranged from 0.856 to 0.996 for CT-P17 and 0.835 to 1.75 for Humira-EU) and C_{max} values.

The local tolerance and antigenicity assessments were included in the repeated-dose toxicity study. Only one female at 32 mg/kg CT-P17 and one female at 32 mg/kg Humira-EU group on Day 29 was detected positive for anti-drug antibodies. The anti-drug-antibody formation did not affect the serum concentration-time profiles on Day 22.

Genotoxicity, Carcinogenicity, Reproduction Toxicity

No comparative carcinogenicity, reproductive and developmental studies were conducted and, in line with the Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues" (EMEA/CHMP/BMWP/403543/2010), are not required.

2.2.4. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, CT-P17 (adalimumab) is not expected to pose a risk to the environment.

2.2.5. Discussion on non-clinical aspects

A stepwise risk-based comparative approach of nonclinical similarity assessment against the reference product Humira-EU has been followed to provide a 'totality of evidence' for demonstrating biosimilarity. Comprehensive biological assays conducted, demonstrated the similar Fab-related biological activities of CT-P17 and Humira-EU engaging with its target TNFα, and the Fc-based functionalities. The glycan profiles were similar. Only some minor variations were observed in the high mannose and afucosylation contents (see also section 2.1. Quality). CT-P17 had slightly higher total afucosylation contents than Humira-EU, but this did not result in differences in the Fc-related functions (binding to FcγRIIIa and ADCC activity). Overall, the functional *in vitro* data demonstrate, that CT-P17 and Humira-EU are similar, and no such quality (e.g. molecular structure, glycosylation profile) or non-clinical (e.g. target receptor binding, functional activity) differences were found that would likely have an impact on the efficacy and/or safety/immunogenicity of the CT-P17 in comparison to the Humira-EU.

To verify the *in vitro* data adequacy, the applicant was asked during the evaluation to provide more information on the *in vitro* pharmacology methods and concentration-effect curves, K_d, EC_{50} or IC_{50} values with the standard errors. This data was asked to be compared head-to-head between CT-P17 (2 FP batches used in the clinical trials and 3 FP batches representative to the final product intended for marketing) and EU Humira batches used in the clinical studies (e.g. $K_{dHumira}$ vs. $K_{dYuflyma}$). In their response, the applicant provided the EC_{50} or Kd values, concentration-effect curves and SPR sensorgrams of each batch of CT-P17 and EU-Humira allowing the verification of *in vitro* reported functional data conclusions. The provided data supported the conclusion, that CT-P17 can be considered biosimilar to the reference product EU-Humira from the non-clinical pharmacology point of view.

The lack of secondary pharmacodynamics, safety pharmacology and pharmacodynamic interaction studies is acceptable.

In addition to the *in vitro* functional studies, one 28-day repeat-dose toxicity study (with TK and immunogenicity testing) in cynomolgus monkeys was conducted. During the assessment, the applicant was asked to comment on the validity of toxicology and toxicokinetic study, because of trace of adalimumab contamination in formulation buffers. After a week on study duration (Day 8), the control animals had already developed anti-adalimumab antibodies, and at day 29 all control animals were positive for anti-CT-P17 and anti-Humira-EU antibodies. Although the applicant investigated the root cause for the contamination, the exact cause was left open. Therefore, the study is considered not to be fully valid for demonstration of toxicological or serum concentration-time profile similarity of CT-P17 and Humira-EU. Nevertheless, this issue was not further pursued by the CHMP since toxicity study provides supplemental information due to the general insensitivity of toxicological studies to reveal the subtle differences and does not have an impact to the overall conclusion on the similarity.

The adequacy of the method to detect anti-drug antibodies in the presence of higher concentrations of free drugs was doubted. However, this issue was not further pursued by the CHMP, as the triggering the antibody

formation in animals against human protein is not predictive and does not affect for the overall conclusion on similarity.

SmPC section 5.3. is identical to that of Humira-EU.

2.2.6. Conclusion on the non-clinical aspects

The side-by-side *in vitro* nonclinical data are paramount for demonstration of biosimilarity from the nonclinical point of view. The functional *in vitro* data demonstrated, that CT-P17 and Humira-EU are similar.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

Table 2 Tabular overview of clinical studies

Type of Study	Study ID	Study Design and Type of Control	Test Product(s); Route of Administration; Dosage Regimen	Objective(s) of the Study	Subjects (N)	Duration of Treatment	Healthy Subjects or diagnosis of patients	Study Status; Type of Report
PK study for biosimilarity	CT-P17 1.1	Phase 1, randomised, double-blind, three-arm, parallel group, single-dose study in healthy male and female subjects	Single dose (40 mg) of either CT-P17, EU-Humira®, or US-Humira® by SC injection via PFS Test product: CT-P17 40 mg/0.4 mL (100 mg/mL) Reference drugs: US-Humira®, 40 mg/0.4 mL (100 mg/mL) EU-Humira®, 40 mg/0.4 mL (100 mg/mL)	**Primary:** To demonstrate the PK similarity in terms of AUC_{0-inf}, AUC_{0-last} and C_{max} **Secondary:** To evaluate the additional PK parameters, safety and immunogenicity	N=312 CT-P17:103 EU-Humira®: 106 US-Humira®: 103	Up to Day 71 (Week 10)	Healthy male or female subjects	Completed CSR CT-P17 1.1
Pilot study	CT-P17 1.2	Pilot Phase 1, randomised, double-blind, two-arm, parallel group, single-dose study in healthy male subjects	Single dose (40 mg) of either CT-P17 or EU-Humira® by SC injection via PFS Test product: CT-P17 40 mg/0.4 mL (100 mg/mL) Reference drug: EU-Humira®, 40 mg/0.4 mL (100 mg/mL)	**Primary:** To evaluate safety in terms of treatment-emergent adverse events (TEAEs) **Secondary:** To evaluate the PK parameters and additional safety including immunogenicity	N=30 CT-P17: 15 EU-Humira®: 15	Up to Day 120 (Week 17)	Healthy male subjects	Completed CSR CT-P17 1.2
PK study between AI and PFS	CT-P17 1.3	Phase 1, randomised, open-label, two-arm, parallel	Single dose (40 mg) of CT-P17 via either AI or PFS Test product:	**Primary:** To demonstrate the PK similarity in terms of AUC_{0-}	N=193 CT-P17 PFS: 95 CT-P17 AI: 98	Up to Day 71 (Week 10)	Healthy male or female subjects	Completed CSR

Type of Study	Study ID	Study Design and Type of Control	Test Product(s); Route of Administration; Dosage Regimen	Objective(s) of the Study	Subjects (N)	Duration of Treatment	Healthy Subjects or diagnosis of patients	Study Status; Type of Report
		group, single-dose study in healthy male and female subjects	CT-P17 40 mg/0.4 mL (100 mg/mL) AI Reference drug: CT-P17 40 mg/0.4 mL (100 mg/mL) PFS	$_{inf}$, $AUC_{0\text{-last}}$ and C_{max} **Secondary:** To evaluate the additional PK parameters, safety and immunogenicity				CT-P17 1.3
Confirmatory efficacy and safety study	CT-P17 3.1	Phase 3, randomised, active-controlled, double-blind , multicentre study in patients with moderate to severe active RA	Multiple single-dose (40 mg) of either CT-P17 or EU-Humira® administered by SC injection via PFS EOW in combination with MTX (between 12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or parenteral [intramuscular or SC] dose) and folic acid (≥ 5 mg/week, oral dose) Prior to dosing at Week 26, all patients will undergo a second randomisation process. Patients in the Humira® treatment group will be randomly assigned in a ratio of 1:1 to either continue Humira or undergo transition to CT-P17 from Week 26 and thereafter up to Week 48. Test product: CT-P17 40 mg/0.4 mL (100 mg/mL) Reference drug: EU-Humira® 40 mg/0.4 mL (100 mg/mL)	**Primary:** To demonstrate similarity of efficacy in terms of clinical response according to ACR20 at Week 24 **Secondary:** To evaluate additional efficacy, PK, PD, usability and overall safety, including immunogenicity and biomarker	N= 648 CT-P17: 324 EU-Humira®: 324	Up to Week 52	Male or female patient with moderate to severe active RA diagnosed according to the 2010 ACR/EULAR classification criteria, despite previous treatment with MTX over at least 12 weeks	Completed CSR CT-P17 3.1
AI usability study	CT-P17 3.2	Phase 3, open-label, single-arm, multiple-dose study in patients with moderate to severe active RA	Multiple dose (40 mg) administered EOW by SC injection via AI from Week 0 to Week 24 in combination with MTX (12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or intramuscular) and folic acid (≥ 5 mg/week, oral dose) Test product: CT-P17 40 mg/0.4 mL (100 mg/mL) AI	**Primary:** The usability as assessed by patients rating using PRE- and POST-Self-Injection Assessment Questionnaire at Week 4 **Secondary:** To evaluate change in usability assessed by patients and observer over time up to Week 24, and overall safety and efficacy	N=62 CT-P17 AI: 62	Up to Week 28	Male or female adult patients with moderate to severe active RA	Completed CSR CT-P17 3.2

Type of Study	Study ID	Study Design and Type of Control	Test Product(s); Route of Administration; Dosage Regimen	Objective(s) of the Study	Subjects (N)	Duration of Treatment	Healthy Subjects or diagnosis of patients	Study Status; Type of Report

ACR20: American College of Rheumatology 20% improvement criteria, AI: auto-injector, $AUC_{0\text{-inf}}$: Area under the concentration-time curve from time zero to infinity, $AUC_{0\text{-last}}$: Area under the concentration-time curve from time zero to last quantifiable serum concentration, C_{max}: Maximum serum concentration, CSR: Clinical study report, EOW: Every other week, MTX: Methotrexate, PD: Pharmacodynamic, PFS: Pre-filled syringe, PK: Pharmacokinetic, Q: Quarter, RA: Rheumatoid arthritis, SC: Subcutaneous

2.3.2. Pharmacokinetics

Pharmacokinetics data were generated in four clinical studies.

- **Study CT-P17 1.1** was the pivotal PK study conducted to demonstrate similar PK between CT-P17 PFS, EU-Humira PFS and US-Humira PFS.
- **Study CT-P17 1.3** was conducted to demonstrate similar PK between CT-P17 PFP (or AI) and PFS devices.
- **Study CT-P17 3.1** was a phase 3, randomised, active-controlled, double-blind study to compare efficacy and safety of CT-P17 PFS with EU-Humira PFS when co-administered with methotrexate (MTX) in patients with moderate to severe active RA. This study provided supportive comparative PK data (trough serum concentrations [C_{trough}] following repeated SC injections).
- **Study CT-P17 1.2**: was a pilot study to evaluate the safety and PK of CT-P17 PFS and EU-Humira PFS. Limited PK data were collected as a secondary endpoint. PK results for study CT-P17 1.2 do not affect the overall assessment of biosimilarity.

Analytical methods

A Meso Scale Discovery - Electrochemiluminescence (MSD-ECL) based method was used in PK studies to quantify CT-P17 and adalimumab (EU-Humira and US-Humira) concentrations in both healthy human serum as well as in RA human serum samples. The assay has been validated according to current guidelines. The assay seems to perform similarly for CT-P17 and the originator in terms of selectivity, precision and accuracy. The applicant has provided an overlay figure representing calibration curves of CT-P17 and EU-and US-Humira.

The immune response after adalimumab administration was also evaluated by the MSD-ECL based method for the detection of ADAs in healthy human serum and RA serum samples. In line with guidelines, a three-tiered approach was used. The methods for healthy and RA samples were similar.

The applicant has used an MSD platform based electrochemiluminescence assay (ECLA) for the evaluation of neutralizing antibodies (NAb). The method was first validated to be used in the clinical study CT-P17 1.2. The NAb-detection method validated for clinical study CT-P17 1.2 was further validated to be used for NAb detection in healthy and RA serum samples (CT-P17 clinical studies 1.1, 1.3 and 3.1). An appropriate method validation following the current guidance was provided. The intra-run, inter-day and inter-run precisions were below 13% and thus acceptable. No matrix interference in healthy or RA serum was observed and drug tolerance was acceptable. Stability studies were presented.

PK Study CT-P17 1.1

Study CT-P17 1.1 is the pivotal comparative PK study. It was a randomised, double-blind, three-arm, parallel group, single-dose study to compare the pharmacokinetics and safety of CT-P17 and Humira (US-licensed Humira and EU-approved Humira) in healthy subjects. Subjects were randomly assigned to one of 3 treatment groups in a 1:1:1 ratio. In each treatment group, all subjects received a single dose (40 mg) of either CT-P17, US-Humira, or EU-Humira by SC injection on Day 1 followed by 10 weeks (70 days) during which PK, safety, and immunogenicity measurements were made. The randomisation to treatment assignment was stratified by baseline body weight (≥80 kg and <80 kg), gender, and study centre. The study drug was administered as a single SC injection via PFS to the subject's lower abdomen (except for the 5 cm around the subject's navel).

The three primary endpoints of the study were $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max}. PK sampling time points were as follows: Study Day 1 pre-dose (within 60 minutes prior to administration of the study drug) and at 6, 12, 24, 48, 72, 96, 108, 120, 132, 144, 168, 192 hours and 14, 21, 28, 42, 56 and 70 days (Study Day 71; end-of-study [EOS]) after the administration. Blood samples for ADA and NAb were taken at baseline (prior to study drug administration on Day 1) and at Study Day 15, 29 and 57 and 71.

A total of 312 subjects were randomised. Four randomised subjects did not receive the study drug. A total of 5 subjects discontinued after study drug administration: 2 subjects were lost to follow-up, 2 subjects due to withdrawal by subject, and 1 subject due to an adverse event (AE).

The PK population consisted of 290 subjects: subjects whose terminal elimination rate constant (λz) could not be estimated as not having at least 3 time points following C_{max} were excluded from the PK population as per protocol. In addition, the extrapolated AUC percentage ($\%AUC_{extrap}$) was required to be ≤ 20% to retain the subject's $AUC_{0\text{-}inf}$ in statistical analysis.

Mean serum concentrations of adalimumab versus time profiles are presented for the PK population in Figure 1. The primary serum PK parameters of adalimumab are summarised by treatment for the PK population in Table 3. Statistical analysis of primary serum PK parameters of adalimumab is summarised by treatment for the PK population in Table 4. Median T_{max} was 167, 167 and 144 h for CT-P17, US-Humira and EU-Humira, respectively. Minimum T_{max} was 48 h for each product.

Since subjects with extrapolated AUC ($\%AUC_{extrap}$) > 20% were not included in the initial PK analysis, upon CHMP's request, the applicant conducted additional statistical analyses of primary PK endpoints ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and C_{max}) for all subjects who received a full dose of study drug. For the analysis of $AUC_{0\text{-}inf}$, only the subjects who had less than 3 time points after C_{max} and $AUC_{0\text{-}inf}$ not calculable were excluded (Table 5).

Results of the initially presented statistical analyses (Table 4) as well as the requested supplementary analyses (Table 5) supported the conclusion of biosimilarity between CT-P17 and the reference products.

Figure 1 Study CT-P17 1.1: Mean (±SD) Serum Concentrations of Adalimumab Versus Time (PK Population)

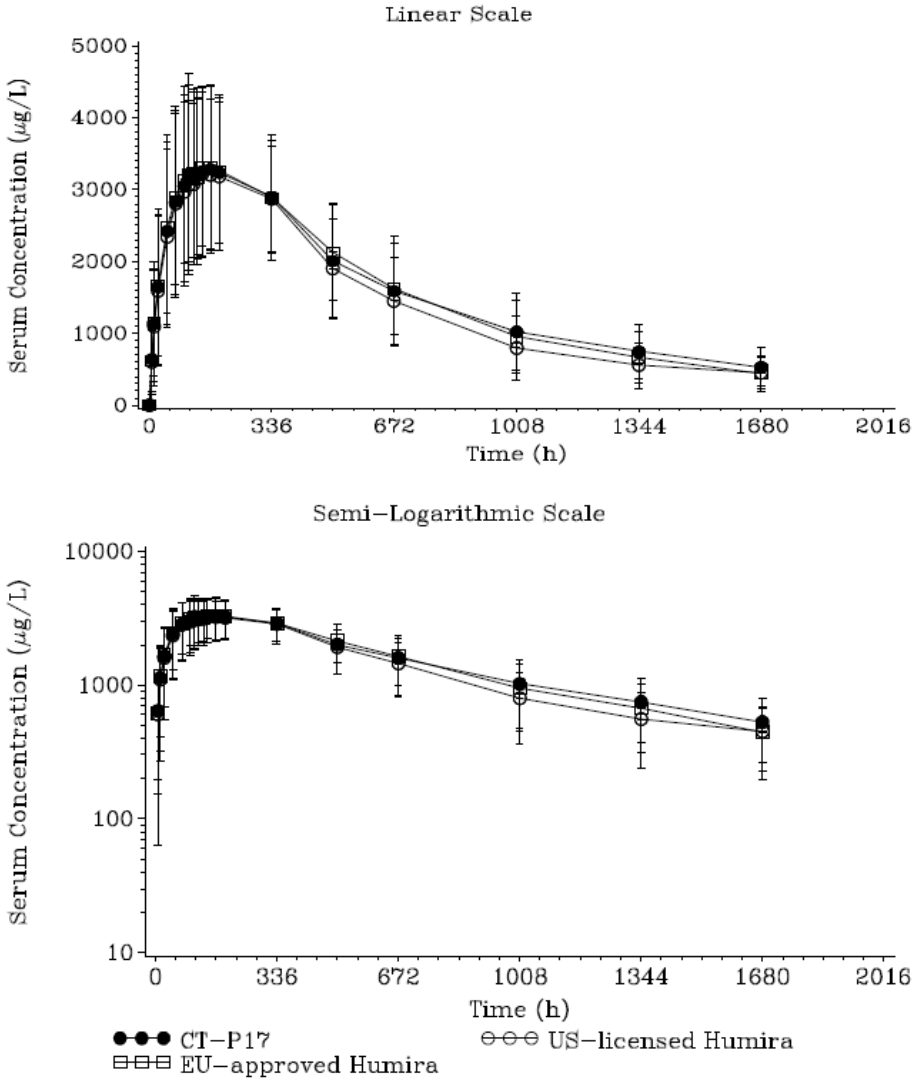


Table 3 Study CT-P17 1.1: Primary PK Parameters of Adalimumab by Treatment Group (PK Population).

PK Parameter (unit) Statistics	CT-P17 (N=97)	US-Humira (N=93)	EU-Humira (N=100)
$AUC_{0\text{-}inf}$ (h•µg/mL)			
n	80	86	89
Mean (SD)	2656.5 (1150.16)	2469.7 (917.47)	2690.6 (943.76)
%CV	43.30	37.15	35.08
Geometric mean	2402.7	2306.8	2529.3
Median	2597.2	2232.3	2575.7
Minimum, Maximum	801, 5817	958, 5209	936, 6008
$AUC_{0\text{-}last}$ (h•µg/mL)			
n	96	93	98
Mean (SD)	2372.7 (954.82)	2185.0 (795.91)	2394.7 (866.95)
%CV	40.24	36.43	36.20
Geometric mean	2165.2	2041.6	2204.7
Median	2278.0	2036.6	2388.8
Minimum, Maximum	530, 4669	869, 4168	319, 5046
C_{max} (µg/mL)			
n	96	93	98
Mean (SD)	3.619 (1.3522)	3.556 (1.1972)	3.660 (1.2212)
%CV	37.367	33.664	33.367
Geometric mean	3.372	3.341	3.454
Median	3.530	3.410	3.465
Minimum, Maximum	1.09, 8.90	1.24, 6.28	1.28, 6.88

Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve from time zero to infinity; $AUC_{0\text{-}last}$, area under the concentration-time curve from time zero to the last quantifiable concentration; C_{max}, maximum serum concentration; %CV, percent coefficient of variation; EU, European Union; PK, pharmacokinetics; SD, standard deviation; US, United States.

Table 4 Study CT-P17 1.1: Statistical Analysis of Primary PK Parameters for Adalimumab by Treatment (ANCOVA, PK Population)

PK Parameter (units)	Treatment	n	Geometric LS Means[a]	Treatment Comparison	Ratio (%) of Geometric LS Means[a]	90% CI[a]
$AUC_{0\text{-}inf}$ (h•µg/mL)	CT-P17	80	2165.0	CT-P17 vs. US-Humira	105.79	(97.19, 115.16)
	US-Humira	86	2046.5	US-Humira vs. EU-Humira	92.63	(85.29, 100.61)
	EU-Humira	89	2209.3	CT-P17 vs. EU-Humira	98.00	(90.06, 106.63)
$AUC_{0\text{-}last}$ (h•µg/mL)	CT-P17	96	1949.2	CT-P17 vs. US-Humira	107.30	(98.29, 117.13)
	US-Humira	93	1816.6	US-Humira vs. EU-Humira	93.93	(86.08, 102.50)
	EU-Humira	98	1933.9	CT-P17 vs. EU-Humira	100.79	(92.42, 109.92)
C_{max} (µg/mL)	CT-P17	96	3.008	CT-P17 vs. US-Humira	101.89	(95.33, 108.89)
	US-Humira	93	2.952	US-Humira vs. EU-Humira	98.20	(91.91, 104.92)
	EU-Humira	98	3.006	CT-P17 vs. EU-Humira	100.05	(93.69, 106.85)

Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve from time zero to infinity; $AUC_{0\text{-}last}$, area under the concentration-time curve from time zero to the last quantifiable concentration; CI, confidence interval; C_{max}, maximum serum concentration; EU, European Union; LS, least squares; PK, pharmacokinetic; US, United States.

Note: An analysis of covariance was performed with the natural log-transformed PK parameters as the dependent variable, treatment as a fixed effect and gender (male or female), Day –1 body weight, and study center as covariates.

$AUC_{0\text{-}inf}$ values were excluded from the statistical analysis after not meeting 1 or more of the following criteria; an adjusted correlation coefficient r^2 of ≥0.85 and a $\%AUC_{extrap}$ ≤20%.

[a] The LS mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of geometric LS means and 90% CIs for the ratios.

Table 5 Study CT-P17 1.1: statistical Analysis of Primary PK parameters of Adalimumab in (ANCOVA) (All Subjects Who Received a Full Dose)

PK Parameter (unit)	Treatment	n	Geometric LS Means	Treatment Comparison	Ratio of Geometric LS Means	90% CI
$AUC_{0\text{-}inf}$ (ug•h/mL)	CT-P17	96	2248.7	CT-P17 vs. EU-Humira	102.16	(93.41, 111.74)
	EU-Humira	100	2201.1	CT-P17 vs. US-Humira	111.06	(101.39, 121.65)
	US-Humira	93	2024.8	US-Humira vs. EU-Humira	91.99	(84.05, 100.68)
$AUC_{0\text{-}last}$ (ug•h/mL)	CT-P17	102	1813.0	CT-P17 vs. EU-Humira	98.21	(88.75, 108.66)
	EU-Humira	104	1846.1	CT-P17 vs. US-Humira	107.12	(96.77, 118.58)
	US-Humira	102	1692.4	US-Humira vs. EU-Humira	91.68	(82.86, 101.43)
C_{max} (ug/mL)	CT-P17	102	2.941	CT-P17 vs. EU-Humira	98.29	(91.85, 105.18)
	EU-Humira	104	2.993	CT-P17 vs. US-Humira	102.72	(95.96, 109.95)
	US-Humira	102	2.863	US-Humira vs. EU-Humira	95.68	(89.42, 102.39)

Source: D120 Section 5.3.5.3 Table 2.10
Note: $AUC_{0\text{-}inf}$ values for subjects having less than 3 time points following C_{max} or $AUC_{0\text{-}inf}$ not calculable were not included.
Abbreviations: ANCOVA, analysis of covariance model; n, number of subjects analysed.

Vast majority of subjects had ADA following the single adalimumab SC injection. The number of ADA negative subjects was 3 (3.1%), 5 (5.4%), 5 (5.0%) within CT-P17, US-Humira, and EU-Humira treatment groups, respectively. An additional ANCOVA analysis was performed in subjects identified as having a positive ADA status and the 90% CIs of the geometric LSM ratios were within the predefined 80% to 125% equivalence margin. Due to the small number of subjects who were negative for ADA, it was not possible to perform the ANCOVA analysis in this subset.

PK Study CT-P17 1.3

This was a randomised, open-label, two-arm, parallel-group, single-dose study, which was designed to compare the PK and safety of the CT-P17 SC administration via AI and PFS in healthy subjects. Enrolled subjects were randomly assigned to 1 of 2 treatment groups in a 1:1 ratio. In each treatment group, all subjects received a single dose (40 mg) of CT-P17 via either AI or PFS on Day 1, followed by 10 weeks during which PK, safety, and immunogenicity measurements were made. The randomisation to treatment assignment was stratified by baseline body weight (≥80 kg and <80 kg), gender, and study centre.

The three primary endpoints of the study were $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max}. PK sampling time points were as follows: Study Day 1 pre-dose (within 60 minutes prior to administration of the study drug) and at 6, 12, 24, 48, 72, 96, 108, 120, 132, 144, 168, 192 hours and 14, 21, 28, 42, 56 and 70 days (Study Day 71; EOS)

after the administration. Blood samples for ADA and NAb were taken at baseline (prior to study drug administration on Day 1) and at Study Day 15, 29 and 57 and 71.

A total of 193 subjects were randomised. Thirteen randomised subjects were discontinued from the study before study drug was administered. In addition to these 13 subjects, a total of 16 subjects were excluded from the PK population: 3 subjects were excluded due to a major protocol deviation and 13 subjects were excluded due to their λz not being estimated as not having at least 3 time points following C_{max}.

The reasons for the major protocol deviations in the 3 subjects were:

- One subject met an exclusion criterion (the subject was dosed with morphine in another clinical trial, but withdrew from that study after Day 15 due to investigator decision shortly after dosing with morphine).
- Two subjects were not fully administered study treatment (the AI was injected into the subject's abdomen, but during the dose the plunger stopped moving and appeared to have stopped pushing in the study drug for both subjects).

The PK population consisted of 164 subjects: subjects whose terminal elimination rate constant could not be estimated as not having at least 3 time points following C_{max} were excluded from the PK population as per protocol. In addition, the extrapolated AUC percentage (%AUC_{extrap}) was required to be ≤ 20% to retain the subject's $AUC_{0\text{-}inf}$ in statistical analysis. During the assessment, the CHMP requested supplementary analyses including these subjects. Statistical analysis using ANOVA model without covariates was also requested as supplementary data.

Mean serum concentrations of adalimumab versus time profiles are presented for the PK population in Figure 2. The primary serum PK parameters of adalimumab are summarised by treatment for the PK population in Table 6. Statistical analysis of primary serum PK parameters of adalimumab is summarised by treatment for the PK population in Table 7. Minimum T_{max} was 24 h and 48 h for CT-P17 AI and CT-P17 PFS, respectively, and median T_{max} was 132 h for both products. The majority of subjects (82 out of 84 subjects in the CT-P17 AI treatment group and 78 out of 80 subjects in the CT-P17 PFS treatment group) had at least one ADA positive post-treatment result. As was done for Study CT-P17 1.1, upon CHMP's request, the applicant conducted an additional statistical analysis to demonstrate PK similarity for all primary PK parameters with all subjects who received a full dose. For the analysis of $AUC_{0\text{-}inf}$, only the subjects who had less than 3 time points after C_{max} and $AUC_{0\text{-}inf}$ not calculable were excluded (Table 8).

Results of the initially presented statistical analyses (Table 6) as well as the requested supplementary analyses (Table 8) supported the conclusion of comparable pharmacokinetics between CT-P17 AI and CT-P17 PFS.

Figure 2 Study CT-P17 1.3: Mean (±SD) Serum adalimumab concentrations (PK Population)

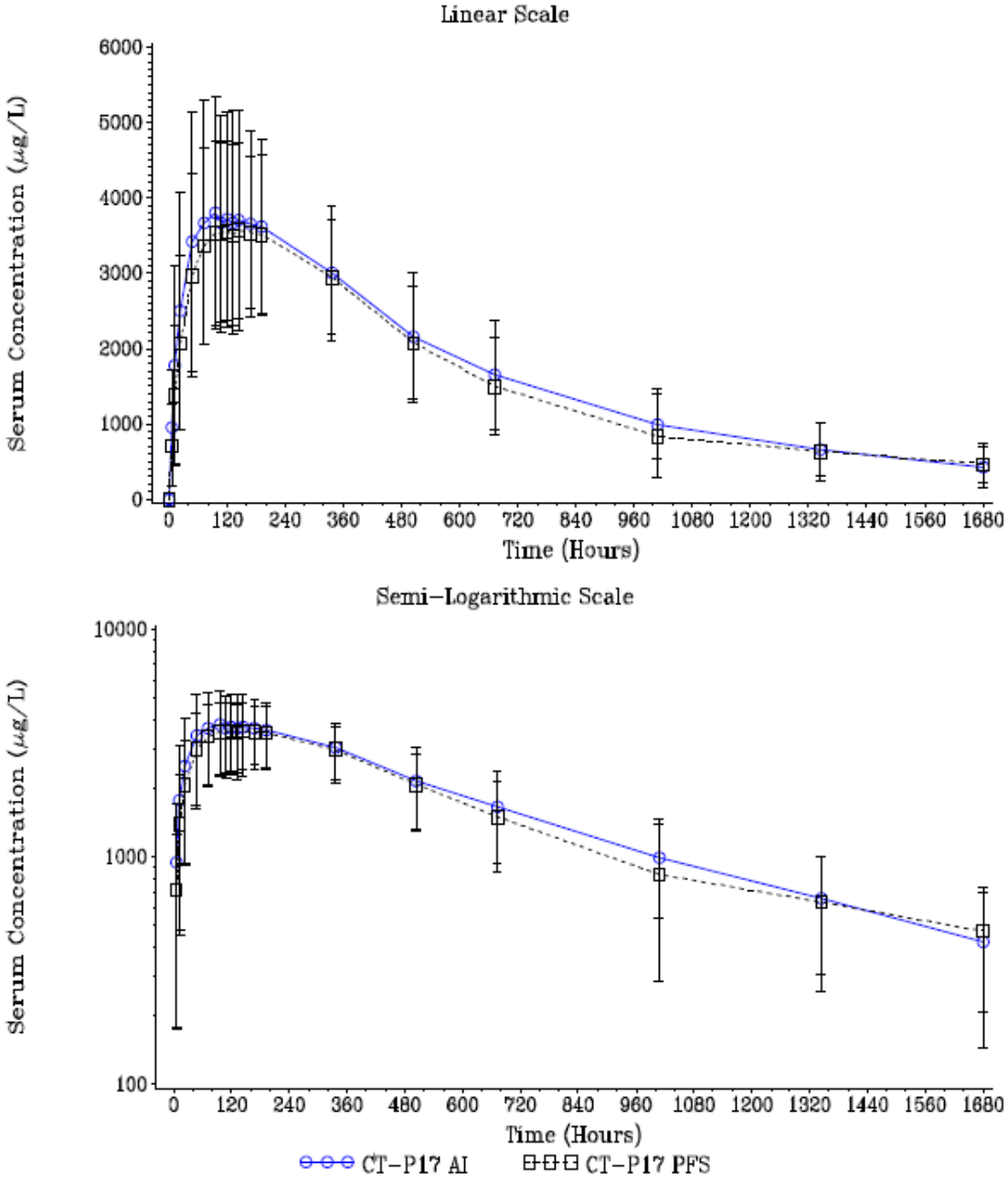


Table 6 Study CT-P17 1.3: Primary PK Parameters of Adalimumab by Treatment Group.

Parameter (unit) Statistics	CT-P17 AI (N=84)	CT-P17 PFS (N=80)
C_{max} (µg/mL)		
n	84	76
Mean (SD)	4.141 (1.5479)	3.908 (1.2620)
%CV	37.381	32.294
Geometric mean	3.863	3.696
Median	3.940	3.835
Minimum, Maximum	1.51, 8.90	1.27, 7.42
$AUC_{0\text{-inf}}$ (h•µg/mL)		
n	69	63
Mean (SD)	2819.5 (945.82)	2684.5 (1031.16)
%CV	33.55	38.41
Geometric mean	2648.9	2516.0
Median	2712.0	2398.1
Minimum, Maximum	867, 5146	1010, 5839
$AUC_{0\text{-last}}$ (h•µg/mL)		
n	84	76
Mean (SD)	2451.3 (1086.28)	2292.9 (1026.99)
%CV	44.31	44.79
Geometric mean	2148.7	2011.1
Median	2407.1	2172.8
Minimum, Maximum	350, 5609	218, 5170

Abbreviations: AI, auto-injector; $AUC_{0\text{-inf}}$, area under the serum concentration-time curve from time 0 to infinity; $AUC_{0\text{-last}}$, area under the serum concentration-time curve from time zero to the last quantifiable concentration; BLQ, below the lower limit of quantitation; C_{max}, maximum serum concentration; %CV, percent coefficient of variation; PFS, pre-filled syringe; SD, standard deviation.

Pharmacokinetic concentrations that were BLQ were set to zero prior to study drug administration and set to missing thereafter. Measurable concentrations after consecutive BLQs during the terminal phase were also set to missing. Four (5.0%) subjects in the CT-P17 PFS treatment group were excluded from the pharmacokinetic summary due to early discontinuation (Section 10.2).

Table 7 Study CT-P17 1.3: Statistical Analysis (ANCOVA) of Primary PK Parameters.

Comparison	PK Parameter (units)	Geometric LSM[(a)]		Ratio (%) of Geometric LSM[(a)]	90% CI[(a)]
		CT-P17 AI	CT-P17 PFS		
CT-P17 AI versus CT-P17 PFS	C_{max} (µg/mL)	(n=84) 3.801	(n=76) 3.705	102.60	(94.08, 111.90)
	$AUC_{0\text{-inf}}$ (h•µg/mL)	(n=69) 2606.4	(n=63) 2514.8	103.64	(93.98, 114.29)
	$AUC_{0\text{-last}}$ (h•µg/mL)	(n=84) 2110.7	(n=76) 2003.4	105.36	(91.09, 121.86)

Abbreviations: AI, auto-injector; ANCOVA, analysis of covariance; $AUC_{0\text{-inf}}$, area under the serum concentration-time curve from time zero to infinity; $AUC_{0\text{-last}}$, area under the serum concentration-time curve from time zero to the last quantifiable concentration; CI, confidence interval; C_{max}, maximum serum concentration; LSM, least squares means; PFS, pre-filled syringe; PK, pharmacokinetic.

n = the number of subjects with non-zero PK values.

An ANCOVA was performed with the natural log-transformed PK parameters as the dependent variable, treatment as a fixed effect and stratification factors (gender [male or female], study center, and body weight as measured on Day –1) as covariates.

$AUC_{0\text{-inf}}$ PK parameter values were excluded from the statistical analysis after not meeting 1 or more of the following criteria; terminal elimination rate constant was calculated with an adjusted correlation coefficient r^2 of ≥0.85 and/or a $\%AUC_{extrap}$ (percentage of the area extrapolated for calculation of area under the concentration-time curve from time zero to infinity) ≤20%.

(a) The LSM differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of geometric LSM (CT-P17 AI/CT-P17 PFS) and 90% CIs for the ratios.

Table 8 Study CT-P17 1.3: statistical Analysis of Primary PK parameters for Adalimumab (ANCOVA) (All Subjects Who Received a Full Dose)

PK parameter (unit)	Treatment	n	Geometric LS Means	Treatment Comparison	Ratio (%) of Geometric LS Means	90% CI
$AUC_{0\text{-inf}}$ (µg•h/mL)	CT-P17 AI	84	2341.4	CT-P17 AI vs. CT-P17 PFS	107.83	93.17 – 124.79
	CT-P17 PFS	80	2171.3			
$AUC_{0\text{-last}}$ (µg•h/mL)	CT-P17 AI	91	1848.8	CT-P17 AI vs. CT-P17 PFS	111.94	92.92 – 134.86
	CT-P17 PFS	87	1651.6			
C_{max} (µg/mL)	CT-P17 AI	91	3.655	CT-P17 AI vs. CT-P17 PFS	103.99	95.34 – 113.42
	CT-P17 PFS	87	3.515			

Source: D120 Section 5.3.5.3 Table 2.12

Abbreviations: AI, auto-injector; ANCOVA, analysis of covariance model; n, number of subjects analysed; PFS, pre-filled syringe.

Efficacy and safety study CT-P17 3.1

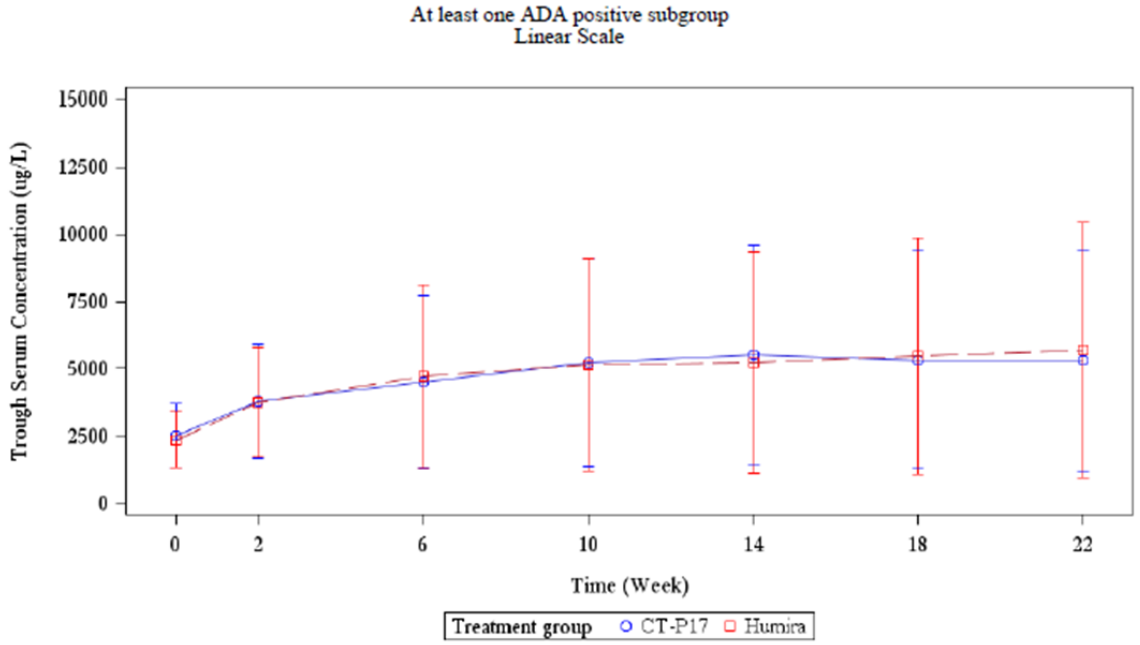
Study CT-P17 3.1 was a randomised, double-blind, study designed to evaluate efficacy and safety of multiple single-doses (40 mg every 2 weeks) of either CT-P17 or EU-Humira administered by SC injection via PFS in combination with MTX in patients with moderate to severe active RA. Serum adalimumab trough levels (C_{trough}) were measured as a secondary endpoint.

The PK population consisted of all patients who received at least one full dose of either of the study drugs and had at least 1 post-treatment adalimumab concentration data. In PK population, patients who show at

least one "Positive" result in immunogenicity test obtained after study drug exposure up to Week 24 were considered as "*at least one ADA positive subgroup*". All patients who only have "Negative" results in post-treatment immunogenicity test up to Week 24 were considered as "*all ADA negative subgroup*".

The mean C_{trough} of adalimumab for both treatment groups in the PK population and by ADA status increased following the first doses and appeared to reach the plateau before week 22 (Figure 3). Adalimumab concentrations were lower in ADA positive subgroup than ADA negative subgroup in both treatment groups. Adalimumab C_{trough} levels are summarised in Table 9 and by ADA status in Table 10. The mean C_{trough} of adalimumab was slightly (9% to 13%) higher in the CT-P17 treatment group compared with the Humira treatment group.

Figure 3 Study CT-P17 3.1: Mean (±SD) Adalimumab C_{trough} by Treatment and ADA Status; PK Population.



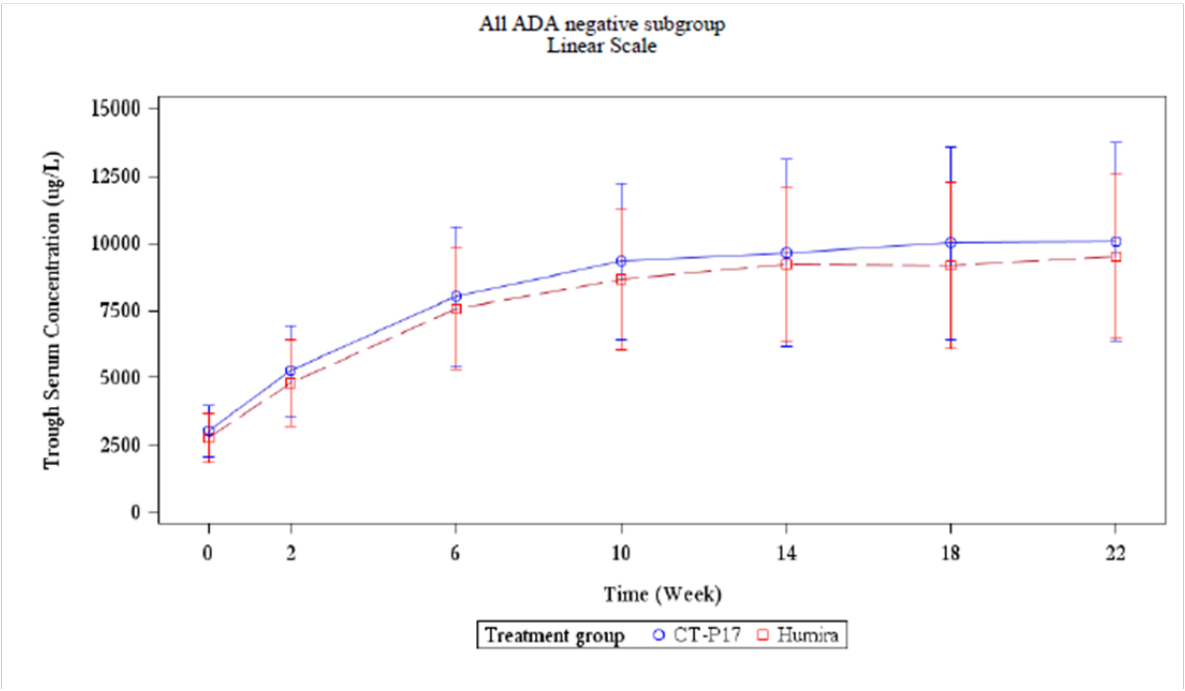


Table 9 Study CT-P17 3.1: Mean (SD) Adalimumab C_{trough} (µg/L); PK Population.

Visit	CT-P17 (N=321)	EU-approved Humira (N=323)
	Mean (SD)	
Week 0	2790.1 (1093.88)	2535.4 (1019.19)
Week 2	4609.9 (2026.10)	4204.1 (1937.42)
Week 6	6476.4 (3384.95)	5955.7 (3288.61)
Week 10	7506.2 (3922.57)	6652.6 (3855.41)
Week 14	7831.7 (4272.83)	6982.4 (4130.99)
Week 18	7979.8 (4449.91)	7093.7 (4294.13)
Week 22	8015.4 (4560.54)	7380.1 (4504.41)

Abbreviation: SD, standard deviation.

Table 10 Study CT-P17 3.1: Mean (SD) Adalimumab C_{trough} (µg/L) by ADA Status; PK Population

Visit	CT-P17 (N=321)	EU-approved Humira (N=323)
	Mean (SD)	
ADA positive subgroup	**N=143**	**N=185**
Week 0	2512.2 (1185.87)	2366.0 (1060.25)
Week 2	3786.8 (2124.59)	3748.2 (2041.30)
Week 6	4508.0 (3235.16)	4720.9 (3399.39)
Week 10	5233.2 (3846.36)	5140.4 (3943.34)
Week 14	5542.7 (4074.01)	5228.2 (4111.68)
Week 18	5336.6 (4053.24)	5471.8 (4398.53)
Week 22	5299.9 (4148.01)	5700.1 (4744.96)
ADA negative subgroup	**N=178**	**N=138**
Week 0	3013.4 (960.50)	2761.3 (917.77)
Week 2	5266.5 (1680.93)	4802.1 (1613.43)
Week 6	8033.3 (2605.05)	7587.2 (2281.08)
Week 10	9332.6 (2901.80)	8668.9 (2625.18)
Week 14	9654.9 (3484.61)	9237.7 (2878.90)
Week 18	10023.6 (3589.67)	9178.9 (3101.94)
Week 22	10083.6 (3701.30)	9524.0 (3055.90)

Abbreviations: ADA, antidrug antibody; BLQ, below lower limit of quantification; LLoQ, lower limit of quantification; SD, standard deviation.

Note: Below lower limit of quantification prior to the first study drug administration (Week 0, Dose 1) was treated as zero (0), and all other BLQ values were set to LLoQ.

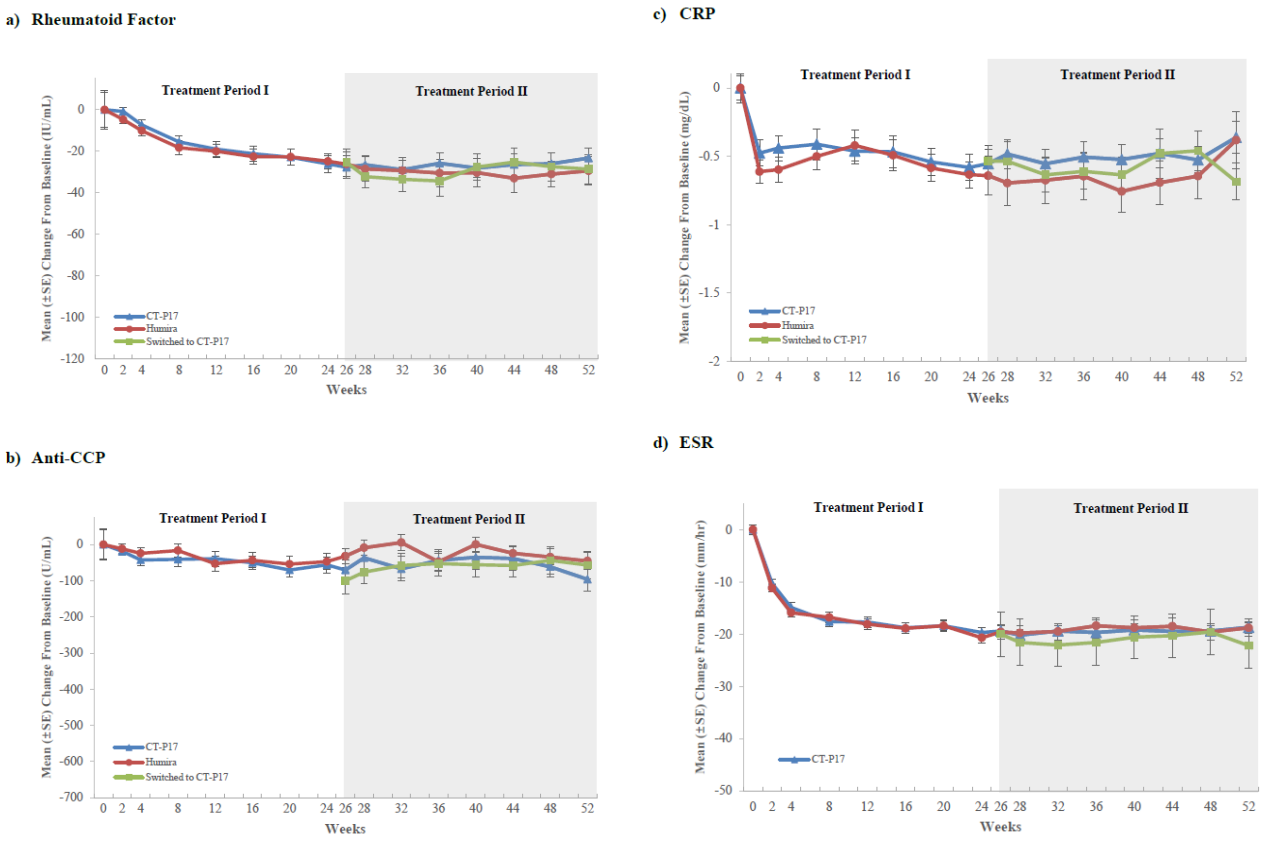
2.3.3. Pharmacodynamics

Validated PD markers do not exist for the efficacy of TNF-α inhibitors and therefore, no pharmacodynamic data were evaluated in the Phase 1 bioequivalence studies in healthy volunteers.

Regarding the primary PD, a set of non-clinical *in vitro* studies have been performed. No studies on secondary PD have been provided, nor have they been required according to the EMA guideline (EMA/CHMP/BMWP/403543/2010).

In the Phase 3 study (CT-P17 3.1), serum concentrations of RF, anti-CCP, CRP, and ESR were assessed as secondary PD endpoints. Upon CHMP's request, the applicant provided graphical presentation (Figure 4). The decreases in RF, anti-CCP, CRP and ESR levels in RA patients were similar up to Week 24 between CT-P17 and EU-approved Humira treatment groups. Some divergence between treatment arms is seen after week 24 (please see Discussion on clinical efficacy).

Figure 4 Mean (±SD) Decreases from Baseline in a) RF, b) anti-CCP, c) CRP and d) ESR in Study CT-P17 3.1 during Overall Period (PD population and PD population – Treatment Period II subset)



2.3.4. Discussion on clinical pharmacology

Analytical methods

All the bioanalytical methods used in the clinical studies for CT-P17 have, in general, been appropriately described and validated according to relevant guidelines. One assay strategy was used both for the determination of CT-P17 and the reference medicinal products (EU-Humira and US-Humira) in serum samples, as well as for evaluation of the immune response after adalimumab administration. The assays seems to perform with similar selectivity and sensitivity for CT-P17 and the reference products.

Pharmacokinetics: CT-P17 vs reference product

Study CT-P17 1.1 was the pivotal study aiming to demonstrate PK similarity of CT-P17 with reference products from the EU and the US. The applicant requested scientific advice (SA) from the CHMP in June 2017. Although the design of the conducted study CT-P17 1.1 is not entirely the same as the design of the study presented in the SA, CHMP concluded that the applicant complied with most recommendations of the advice.

The parallel-group design, study population (healthy volunteers) and posology (single 40 mg SC injection) are acceptable to the CHMP and compliant with the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010). Duration of PK sampling (70 days following the drug injection) was considered in the SA to be adequate to cover the typical elimination period of adalimumab; however, it was also noted by the CHMP that the duration should capture approximately 80% of $AUC_{0\text{-}inf}$. Immunogenicity sampling was conducted in accordance with the SA. The primary endpoints ($AUC_{0\text{-}inf}$, C_{max}, $AUC_{0\text{-}last}$) and covariates (gender, body weight, study centre) included in the ANCOVA model are acceptable to the CHMP. However, definition of the PK population, especially exclusion of subjects with extrapolated AUC ($\%AUC_{extrap}$) > 20%, was deemed not appropriate to the CHMP and additional statistical analyses were requested.

In the initial statistical analyses for $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% when comparing CT-P17 with the reference product from EU as well as from US. Results for the additional analyses were in agreement with the initial analyses and supported the conclusion of biosimilarity.

Study CT-P17 3.1 was a randomised, active-controlled, double-blind study designed to compare efficacy and safety of CT-P17 PFS with EU-Humira PFS when co-administered with MTX in patients with moderate to severe active RA. This study provided supportive comparative PK data (trough serum concentrations [C_{trough}] following repeated SC injections) in a target patient population. The mean C_{trough} of adalimumab was generally higher in the CT-P17 treatment group over the first 24 weeks of study CT-P17 3.1, but the overall variability was high in both treatment groups. In both CT-P17 and Humira treatment groups, patients with ADA had markedly lower C_{trough} levels compared with patients without ADA. High ADA titre was also associated with lower C_{trough} levels; see section Clinical safety / Immunological events of this assessment report.

Pharmacokinetics: AI vs PFS

The primary aim of study CT-P17 1.3 was to demonstrate similar exposure to adalimumab following SC administration via applicant's AI and PFS devices. The parallel-group design, study population, posology and the primary PK parameters ($AUC_{0\text{-}inf}$, C_{max}, $AUC_{0\text{-}last}$) are acceptable to the CHMP. However, definition of the PK population, especially exclusion of subjects with extrapolated AUC ($\%AUC_{extrap}$) > 20%, was deemed not appropriate and additional statistical analyses were requested.

For $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} the 90% confidence interval for the ratio of the AI and the PFS devices fell within the conventional acceptance range of 80.00-125.00%. Results for the additional analyses supported the conclusion of comparable pharmacokinetics between CT-P17 AI and CT-P17 PFS.

Pharmacodynamics

No pharmacodynamic data were evaluated in healthy volunteers and none is required. Primary PD was assessed in a set of non-clinical *in vitro* studies. Results from non-clinical studies support similarity (see section 2.2. non-clinical assessment). Secondary PD endpoints were assessed in study CT-P17 3.1 in RA patients (see section 2.4. clinical efficacy).

Product information

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

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology data support the conclusions of biosimilarity of CT-P17 to the EU reference product (Humira) and of comparable pharmacokinetics following administration of CT-P17 via AI and PFS.

2.4. Clinical efficacy

2.4.1. Main study

Study CT-P17 3.1: A phase 3, randomised, active-controlled, double-blind, multicentre study designed to evaluate efficacy, PK, PD, usability, overall safety and immunogenicity of multiple single-doses (40 mg) of either CT-P17 or EU-Humira administered by SC injection via PFS in combination with MTX in patients with moderate to severe active RA.

PK, PD, immunogenicity, efficacy, safety and usability data up to Week 24 were submitted at D0. Upon CHMP's request, the full study report, up to week 52, was submitted during the procedure.

Methods

Study Participants

The main inclusion criteria are listed below:

1. Patient was male or female between 18 to 75 years old, both inclusive.
2. Patient had a diagnosis of RA according to the 2010 ACR/EULAR classification criteria (Aletaha *et al.,* 2010[1]) for at least 24 weeks prior to the first administration of the study drug (Day 1).
3. Patient 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.
4. Patient had been receiving oral or parenteral MTX at a dose of between 12.5 to

[1] Aletaha, Daniel, et al. "2010 rheumatoid arthritis classification criteria: an American College of Rheumatology / European League Against Rheumatism collaborative initiative." Arthritis & Rheumatism 62.9 (2010): 2569-2581.

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 (Day 1).

5. Patient had adequate renal and hepatic function at Screening as defined by the following clinical chemistry results:
   - Serum creatinine ⩽1.5 × upper limit of normal (ULN) or an estimated creatinine clearance level >50 mL/min (by Cockcroft-Gault formula) (System International [SI] units: 0.84 mL/s)
   - Serum alanine aminotransferase ⩽3.0 × ULN
   - Serum aspartate aminotransferase ⩽3.0 × ULN
   - Serum total bilirubin ≤1.5 × ULN
6. Patient had the following haematology laboratory test results at Screening:
   - Haemoglobin >8.0 g/dL (SI units: >80 g/L or 4.96 mmol/L)
   - Absolute neutrophil count ⩾1.5 × 10^3 cells/µL (SI units: ⩾1.5 × 10^9 cells/L)
   - Platelet count ⩾75 × 103 cells/µL (SI units: ⩾75 × 109 cells/L)

Patients, who had previously received biologic or targeted synthetic DMARDs (e.g., tofacitinib, baricitinib) for the treatment of RA and/or TNF-α inhibitor for any purposes, were excluded. Exclusion criteria were in accordance with warnings and contraindications in the SmPC of Humira.

Treatments

Treatment Period I (from Week 0 to Week 24)

Patients were randomised in a 1:1 ratio to receive either CT-P17 (40 mg/0.4 mL) or EU-Humira (40 mg/0.4 mL) up to Week 24 as a SC injection via PFS every other week (EOW). In addition, all patients received MTX (between 12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose), and folic acid (⩾5 mg/week, oral dose).

Treatment Period II (after Week 24 to Week 48)

Prior to dosing at Week 26, patients underwent the second randomisation process. Patients who were initially randomly assigned to EU-approved Humira were randomised 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.

The total duration of the study was 58 weeks (per protocol), 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.

Objectives

The primary objective of this study was to demonstrate that CT-P17 is equivalent to EU-approved Humira, in terms of efficacy as determined by clinical response according to the American College of Rheumatology definition of a 20% improvement (ACR20) at Week 24.

The secondary objective was to evaluate additional efficacy, PK, PD, and overall safety, including immunogenicity and biomarker data, and device usability (Bulgaria and Poland only).

Upon request, the null hypothesis and the alternative hypothesis for the primary efficacy endpoint were specified as below:

$H_0: |pp_{tt} - pp_{rr}| \geqslant 0.15, Ha: |pp_{tt} - pp_{rr}| < 0.15$

where pp_{tt} is a response rate for CT-P17, and pp_{rr} is a response rate for EU-Humira.

Outcomes/endpoints

The primary efficacy endpoint of study CT-P17 3.1 was the proportion of patients achieving clinical response according to the ACR20 at Week 24 in the intent-to treat (ITT) population. Equivalence was defined as a 95% CI for the estimate of treatment difference entirely within the predefined equivalence margin of -15% to 15%.

Secondary efficacy endpoints were 50% improvement of ACR (ACR50), 70% improvement of ACR (ACR70) and hybrid ACR response, individual components of ACR, Disease Activity Score using 28 joint counts (DAS28 [ESR] score, DAS28 [CRP] score, and individual components), EULAR response criteria, clinical disease activity index (CDAI), simplified disease activity index (SDAI), quality of life (36-item short form health survey [SF-36]), and joint damage progression.

Safety, immunogenicity and device usability were also assessed as secondary endpoints.

Sample size

A sample size of 450 patients (225 patients in each treatment group of CT-P17 and EU-approved Humira) led to 83% statistical power for the demonstration of similarity of ACR20 at Week 24 based on the expected ACR20 rate of 64% with an equivalence margin of -15% to 15% using a two one-sided 2.5% significance level of an equivalence test. The drop-out rate had been hypothesised at 20%; therefore, approximately 564 patients (282 patients in each treatment group of CT-P17 and EU-approved Humira) were to be randomised.

Randomisation and blinding (masking)

Patients were randomly assigned at Day 1 (Week 0) to receive CT-P17 or EU-approved Humira using a 1:1 allocation ratio. The randomisation to treatment assignment was stratified by the following:

- Country
- Disease activity by simplified disease activity index (SDAI) at Screening; high (SDAI >26) versus not high (SDAI ≤26)

Patients received CT-P17 or EU-approved Humira EOW up to Week 24. Prior to dosing at Week 26, patients in the EU-approved Humira treatment group were randomly assigned in a ratio of 1:1 to either continue EU-approved Humira (Cohort 2) or undergo transition to CT-P17 (Cohort 3) from Week 26. All patients who were initially randomly assigned to CT-P17 at Day 1 (Week 0) continued their treatment with CT-P17 (Cohort 1) until EOS. The second randomisation was also conducted in Cohort 1 prior to dosing at Week 26 to maintain the study blind.

The second randomisation to Cohorts 2 or 3 was stratified by the following:

- Disease activity by SDAI at Week 24; remission (SDAI ≤3.3) versus non-remission (SDAI >3.3)

The appropriate number of study drug syringes was allocated to each patient. A tear-off label was attached to the outside of each patient kit, as well as to the immediate container. The text was in compliance with the local regulatory requirements and included some of the following information: protocol number, patient number/study centre number, contents and quantity, lot number, randomisation code/kit number, investigator's name, storage instructions, caution statement, Celltrion Inc.'s contact and address, expiry date.

Statistical methods

The populations for main efficacy analyses were ITT and per-protocol (PP) population.

The ITT population consisted of 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.

The PP population consisted of all randomly assigned patients who had received all full doses of study drug up to Week 22 (total of 12 injections) and had an ACR assessment at Week 24. If a patient received all doses of study drug up to Week 22 (total of 12 injections), but delayed study drug administration more than 7 days from the previous dosing, before Week 24, then the patient was excluded from PP population. A major protocol deviation that could affect the interpretation of study results of primary efficacy endpoint was excluded from the PP population. Final determinations of the PP population were made at the blinded data review meeting (DRM) held in accordance with ICH harmonised tripartite guideline E9.

Efficacy Evaluation

Primary efficacy endpoint analysis was performed by treatment group between the CT-P17 and EU-approved Humira using the ITT and PP populations. All secondary efficacy endpoint analyses up to Week 24 were performed by treatment group, between the CT-P17 and EU-approved Humira treatment groups, using the ITT and PP populations.

Primary Efficacy Analysis

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 centre for the evaluation of ACR20 at the week of interest.

The analysis of the primary efficacy endpoint was conducted by the exact binomial approach using a Farrington-Manning score method (Chan and Zhang, 1999[2]; Inverting two one-sided test), and the 95% CI for the difference in proportion between the 2 treatment groups was produced. Therapeutic equivalence of clinical response according to ACR20 criteria was concluded if the 95% CIs for the treatment difference were entirely within the limits of -15% to 15% at Week 24. The primary efficacy endpoint was analysed using the ITT and PP populations. The ITT population was the predefined primary population for the primary endpoint.

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.

[2] Chan, Ivan SF, and Zhongxin Zhang. "Test - based exact confidence intervals for the difference of two binomial proportions." Biometrics 55.4 (1999): 1202-1209.

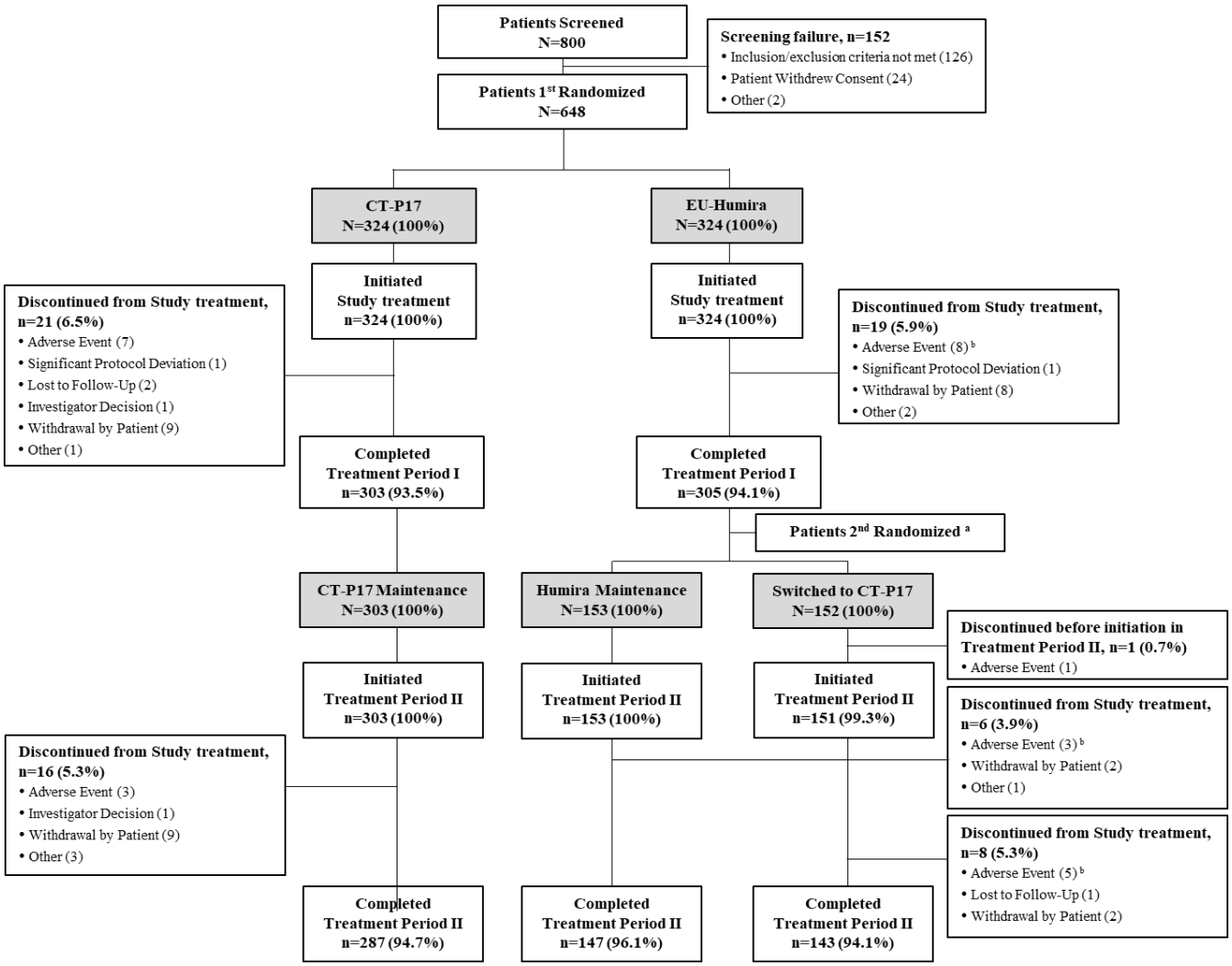
Results

In total, 648 patients were randomised to receive either CT-P17 or EU-Humira (Figure 5).

In Treatment Period II, 608 patients were randomly assigned to study drug and 607 patients initiated the study treatment in Treatment Period II (303 [100.0%] patients, 153 [100.0%] patients, and 151 [99.3%] patients in the CT-P17 maintenance, Humira maintenance, and switched to CT-P17 groups, respectively) (Figure 5).

Participant flow

Figure 5 Participant flow in study CT-P17 3.1



Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.
[a] Prior to dosing at Week 26, all patients underwent the second randomisation process. Patients who were initially randomly assigned to EU-approved Humira were randomised 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.
[b] The numerical difference between patients who discontinued the study treatment due to AE in patient disposition and summary of TEAE leading to discontinuation is due to the fact that patient disposition's summary was based on the number of patients discontinued in each treatment period and the summary of TEAE leading to discontinuation was based on the start date of AE.

Recruitment

First patient randomly assigned to treatment: 05 December 2018.

Last patient last visit: 24 April 2020.

Conduct of the study

The original protocol (Version 1.0), dated 10 May 2018, was amended 7 times during the course of the study.

- 2 Global protocol amendments
    - First amendment dated 11 July 2018 (Version 2.0 - prepared but not submitted)
    - Second amendment, dated 06 August 2018 (Version 3.0 - submitted and approved)
- 5 Country-specific protocol amendments

Baseline data

Baseline characteristics of the study population are described in Table 11.

Table 11 Demographics and Stratification Details in study CT-P17 3.1: ITT Population

	CT-P17 (N=324)	EU-approved Humira (N=324)	Total (N=648)
Age (years)			
n	324	324	648
Mean (SD)	52.0 (12.11)	51.8 (11.80)	51.9 (11.95)
Median	53.5	54.0	54.0
Min, max	18, 75	19, 75	18, 75
Gender, n (%)			
Male	75 (23.1)	59 (18.2)	134 (20.7)
Female	249 (76.9)	265 (81.8)	514 (79.3)
Female fertility status [a], n (%)			
Surgically sterilised	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)			
n	324	324	648
Mean (SD)	165.09 (9.206)	165.43 (8.721)	165.26 (8.961)

Median	164.0	164.0	164.0
Min, max	146.0, 204.0	146.0, 194.0	146.0, 204.0
Screening Weight (kg)			
n	324	324	648
Mean (SD)	72.64 (14.270)	73.23 (14.163)	72.94 (14.209)
Median	71.0	71.0	71.0
Min, max	41.0, 144.0	47.0, 111.7	41.0, 144.0
Screening BMI (kg/m^2)			
n	324	324	648
Mean (SD)	26.574 (4.2114)	26.686 (4.2781)	26.630 (4.2420)
Median	26.110	26.180	26.140
Min, max	15.06, 35.60	17.65, 34.89	15.06, 35.60
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)

Abbreviations: BMI, body mass index; ITT, intent-to-treat; max, maximum; min, minimum; SD, standard deviation; SDAI, simplified disease activity index. Note: Height, weight and BMI results summarized were the screening assessment values. [a] Percentages were calculated by using the number of female patients as the denominator.

Baseline RA characteristics:

The mean (SD) time since RA diagnosis was 6.79 (6.76) years in the CT-P17 treatment group and 6.59 (6.81) years in the EU-approved Humira treatment group.

The mean (SD) dose of MTX taken at first study drug administration was similar between the 2 treatment groups (18.9 [4.46] mg/week for the CT-P17 treatment group and 18.4 [4.37] mg/week for the EU-approved Humira treatment group).

In addition to MTX, the most frequently reported concomitant medication in treatment period I, by drug class, was corticosteroids for systemic use (170 [52.5%] patients in the CT-P17 treatment group and 177 [54.6%] patients in the EU-approved Humira treatment group), followed by anti-inflammatory and antirheumatic products (151 [46.6%] patients in the CT-P17 treatment group and 153 [47.2%] patients in the EU-approved Humira treatment group).

Table 12 Analysis Populations in study CT-P17 3.1 TP I

	CT-P17 (N=324)	EU-approved Humira (N=324)	Total (N=648)
	Number (%) of patients		
Intent-to-Treat Population	324 (100.0)	324 (100.0)	648 (100.0)
ITT Population - at least one ADA positive subgroup	143 (44.1)	185 (57.1)	328 (50.6)
ITT Population - all ADA negative subgroup	178 (54.9)	138 (42.6)	316 (48.8)
Per-Protocol Population	285 (88.0)	276 (85.2)	561 (86.6)
PP Population - at least one ADA positive subgroup	124 (38.3)	151 (46.6)	275 (42.4)
PP Population - all ADA negative subgroup	161 (49.7)	125 (38.6)	286 (44.1)
Pharmacokinetic Population	321 (99.1)	323 (99.7)	644 (99.4)
Pharmacodynamic Population	321 (99.1)	323 (99.7)	644 (99.4)
Usability Population	70 (21.6)	76 (23.5)	146 (22.5)
Safety Population	324 (100.0)	324 (100.0)	648 (100.0)

Abbreviations: ADA, anti-drug antibody; ITT, intent-to-treat; PP, per protocol. Note: Percentages were based on the number of patients in the ITT population per treatment group and overall. A total of 4 patients (3 patients in the CT-P17 and 1 patient in the EU-Humira) in the ITT population with no posttreatment ADA results were not included in either of the ADA subgroups.

Table 13 Analysis in study CT-PT17 3.1 TP II

	CT-P17 Maintenance (N=303)	Humira Maintenance (N=153)	Switched to CT-P17 (N=152)	Total (N=608)
Subset	Number (%) of patients			
ITT population - Treatment Period II	303 (100.0)	153 (100.0)	152 (100.0) [c]	608 (100.0)
PP population - Treatment Period II	282 (93.1)	138 (90.2)	134 (88.2)	554 (91.1) [a]
PK population - Treatment Period II	302 (99.7)	152 (99.3)	149 (98.0)	603 (99.2)
PD population - Treatment Period II	302 (99.7)	152 (99.3)	150 (98.7)	604 (99.3)
Safety population - Treatment Period II	303 (100.0)	153 (100.0) [b]	151 (99.3)	607 (99.8)

Abbreviations: ITT, intent-to-treat; PD, pharmacodynamics; PK, pharmacokinetic; PP, per protocol.
Note: Percentages were based on the number of patients in the ITT population – Treatment Period II subset per treatment group and overall.
[a] 4 patients excluded due to major protocol deviation (two patients: misrandomisation) and other reason for exclusion from PP (one patient: no study drug received, one patient: no post treatment efficacy assessment) , 50 patients were excluded from PP population – Treatment Period II subset as they were already excluded from the PP population.
[b] One patient (EU-Humira in Treatment Period I) was planned to be randomised to Humira maintenance group, but actually received CT-P17 at Week 28, and therefore, included in the Humira maintenance group in this table but included in the switched to CT-P17 group for the safety summary.
[c] One patient (EU-Humira in Treatment Period I) was randomised to switched to CT-P17 group at Week 26, but did not receive any study drug in Treatment Period II.

Numbers analysed

Outcomes and estimation

Primary endpoint

The primary efficacy endpoint was the ACR20 response rate at Week 24. The 95% CI for the estimate of treatment difference was entirely within the predefined equivalence margin of -15% to 15% (Table 14).

Table 14 ***Proportion of Patients Achieving Response According to ACR20 at Week 24***

Treatment Group	ACR20 Response Rate	Treatment Difference Estimate (%) [a]	95% CI of Treatment Difference (%) [a]
ITT Population			
CT-P17	268/324 (82.72%)	0.00	(-5.94, 5.94)
EU-approved Humira	268/324 (82.72%)		
PP population			
CT-P17	248/285 (87.02%)	0.06	(-5.60, 5.78)
EU-approved Humira	240/276 (86.96%)		

Abbreviations: ACR, American College of Rheumatology; ACR20, ACR 20% improvement criteria; CI, confidence interval; ITT, intent-to-treat; PP, per protocol. Note: Patients who terminated from 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. [a] Estimate of the difference in proportion and 95% CI between the two treatment groups were estimated using the exact binomial method using a Farrington-Manning score method.

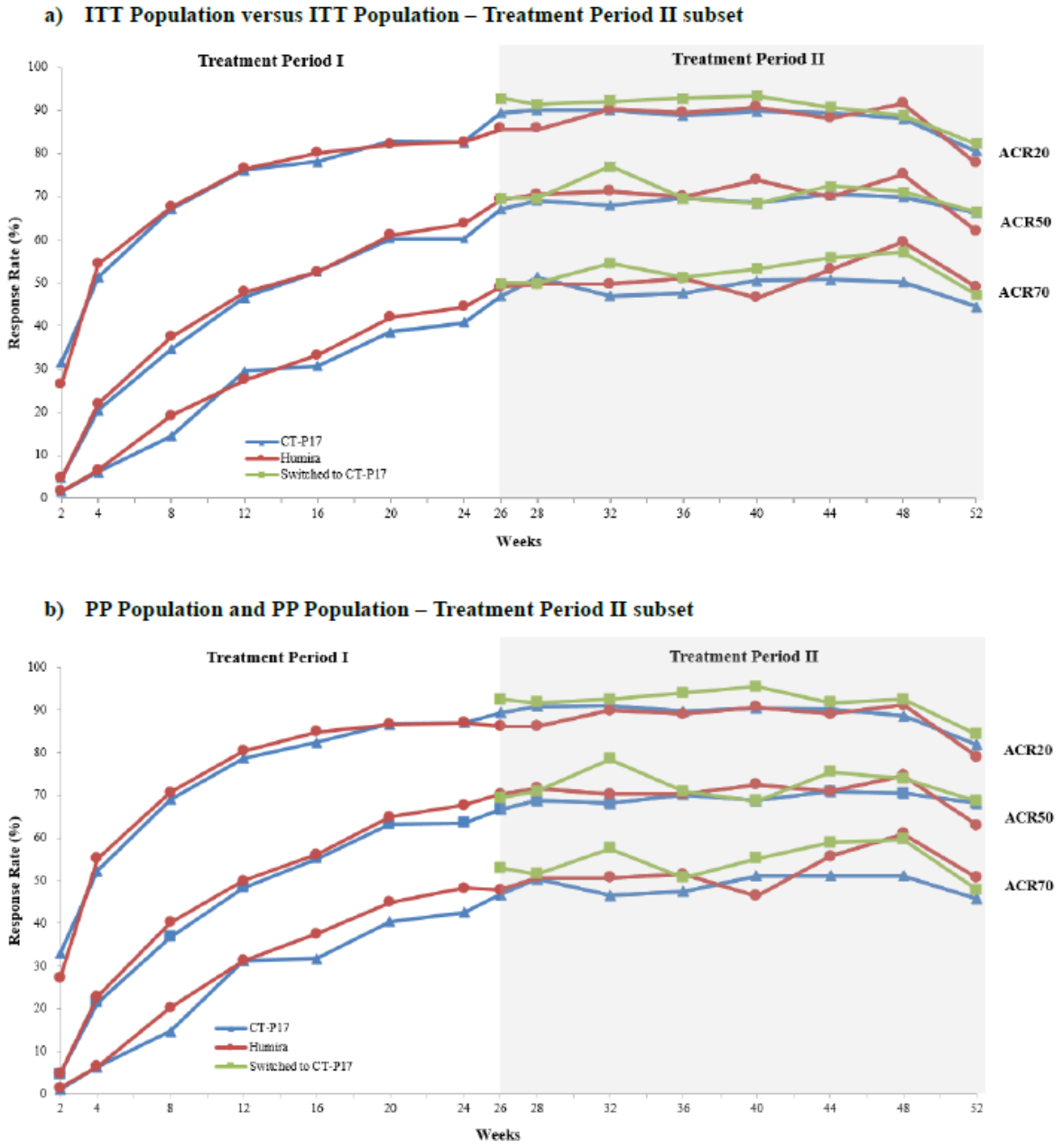
The sensitivity analysis rendered similar results. The 95% CI for the estimate of treatment difference estimated from the logistic regression using treatment group as a fixed effect, and country and disease activity by SDAI at screening as covariates was -5.75 to 5.86 for the ITT population and -5.07 to 5.93 for the PP population.

Hence, the primary objective of this trial was met and the results were unchanged after controlling for country and disease activity.

Secondary endpoints

The proportions of patients achieving response according to the ACR20, ACR50, and ACR70 criteria seemed similar at all time points up to Week 52 between the CT-P17 and EU-approved Humira treatment groups in both the ITT and PP populations. Results are presented in Figure 6 and Table 15.

Figure 6 Proportions of Patients Achieving Response according to ACR Criteria ACR20/50/70 in Study CT-P17 3.1 during Overall Period (ITT and PP Populations and ITT and PP Populations – Treatment Period II Subsets)



In treatment period I (up to week 24), the estimate of treatment difference in ACR20, ACR50 and ACR70 response rates between treatment arms was small, ranging from -5.8% to 4.9% with 95% CI remaining within +/- 15% in both the ITT and the PP populations at all time points (Table 15).

In treatment period II (weeks 26 to 52), the 95% CIs were wider. Nevertheless, estimates of difference between treatment arms were small and most of the 95% CIs remained within +/- 15% in both the ITT and the PP populations at all time points. No statistically significant differences were seen at any time point (data not shown).

Table 15 Estimated Difference (95% CI of Difference) of Proportion of Patients Achieving Response according to ACR Criteria (ACR20/50/70) in Study CT-P17 3.1 during Treatment Period I (ITT and PP Populations)

Population Visit	Efficacy Parameter	Treatment Group, n (%)		Estimate of Treatment Difference[1]	95% CI of Treatment Difference[1]
		CT-P17	EU-Humira		
ITT Population					
Week 2	ACR20	102 (31.5)	86 (26.5)	4.94	(-2.04, 11.94)
	ACR50	15 (4.6)	15 (4.6)	0.00	(-3.24, 3.24)
	ACR70	5 (1.5)	5 (1.5)	0.00	(-1.90, 1.90)
Week 4	ACR20	166 (51.2)	176 (54.3)	-3.09	(-10.77, 4.60)
	ACR50	66 (20.4)	71 (21.9)	-1.54	(-7.83, 4.74)
	ACR70	20 (6.2)	21 (6.5)	-0.31	(-4.06, 3.44)
Week 12	ACR20	247 (76.2)	248 (76.5)	-0.31	(-6.85, 6.23)
	ACR50	151 (46.6)	155 (47.8)	-1.23	(-8.92, 6.45)
	ACR70	96 (29.6)	89 (27.5)	2.16	(-4.79, 9.11)
Week 24	ACR20	268 (82.7)	268 (82.7)	0.00	(-5.82, 5.82)
	ACR50	195 (60.2)	206 (63.6)	-3.40	(-10.87, 4.08)
	ACR70	132 (40.7)	144 (44.4)	-3.70	(-11.31, 3.91)
PP Population					
Week 2	ACR20	94 (33.0)	75 (27.2)	5.81	(-1.76, 13.38)
	ACR50	13 (4.6)	13 (4.7)	-0.15	(-3.63, 3.33)
	ACR70	3 (1.1)	4 (1.4)	-0.40	(-2.24, 1.45)
Week 4	ACR20	149 (52.3)	152 (55.1)	-2.79	(-11.04, 5.46)
	ACR50	61 (21.4)	63 (22.8)	-1.42	(-8.29, 5.45)
	ACR70	18 (6.3)	18 (6.5)	-0.21	(-4.26, 3.85)
Week 12	ACR20	224 (78.6)	222 (80.4)	-1.84	(-8.51, 4.84)
	ACR50	138 (48.4)	138 (50.0)	-1.58	(-9.85, 6.70)
	ACR70	89 (31.2)	86 (31.2)	0.07	(-7.60, 7.74)
Week 24	ACR20	248 (87.0)	240 (87.0)	0.06	(-5.51, 5.63)
	ACR50	181 (63.5)	187 (67.8)	-4.24	(-12.10, 3.61)
	ACR70	121 (42.5)	133 (48.2)	-5.73	(-13.96, 2.49)

Abbreviations: ACR20, American College of Rheumatology 20% improvement criteria; ACR50, American College of Rheumatology 50% improvement criteria; ACR70, American College of Rheumatology 70% improvement criteria; ITT, intent- to-treat; PP, per-protocol.

Note: Percentages are calculated by using the number of patients in the population as the denominator. The 95% CI of the difference of ACR response proportion between two treatment groups is calculated using the asymptotic method.

[1] The difference in proportion and 95% confidence interval between the two treatment groups is estimated using the exact binomial method using a Farrington-Manning score method.

All individual components of the ACR criteria as well as the hybrid ACR response measure rendered similar response between treatment groups across different visit time points in both ITT and PP populations.

The actual values and changes from baseline of DAS28(CRP) and DAS28(ESR) over time across different visit time points in both ITT and PP populations were similar between treatment arms. The difference between the mean changes from baseline in DAS28(CRP) at different visit time points did not exceed 0.6 in DAS28(CRP) score, generally approved to be the minimal difference of clinical importance. At week 24, the 95% CI for the estimate of treatment difference in DAS28(CRP) was entirely within the margin of clinical significance ±0.6% in both the PP and the ITT populations at all time points (Table 16). Similar efficacy was maintained also after switching to CT-P17 at week 26 and up to week 52.

Table 16 Analysis of Change from Baseline of DAS28 (CRP) at Week 24 (ANCOVA) ITT Population

Treatment	**n**	**LS mean (SE)**	**Estimate of treatment difference**	**95% CI of treatment difference**
CT-P17	309	-2.54 (0.099)	-0.01	(-0.19, 0.16)
Humira	312	-2.52 (0.098)		

Analysis of covariance (ANCOVA) was used for comparing the change from baseline of DAS28(CRP) at Week 24 between two groups (CT-P17 and Humira), considering the treatment group as a fixed effect and country and disease activity by simplified disease activity index (SDAI) at screening as covariates. Adjusted least squares means and standard error, estimate of treatment difference [CT-P17 - Humira] and 2-sided 95% confidence interval calculated from the ANCOVA model.

The results from all supportive secondary efficacy endpoints were similar between treatment arms.

Ancillary analyses

To examine the impact of FcγR genotype on efficacy response to CT-P17 and EU-Humira, ACR20 results by genotype up to Week 24 from Study CT-P17 3.1 were evaluated as *post-hoc* analyses, and the patients were analysed by genotype and treatment group. Patients' polymorphism regarding the FcγRIIa and FcγRIIIa gene were evenly distributed in the two treatment groups. The proportions of patients achieving response according to ACR20 at Week 24 by genotype were comparable between the treatment arms when comparing the same genotype. The response proportion was more than 80% in all subgroups. However, the sample size in some genotype constellation was too small to draw a definite corollary.

Subgroup analysis was also performed in the ADA subgroups to examine the impact of ADA on efficacy in terms of ACR20/50/70. The results are presented and discussed in the safety section 2.5. "Immunological events".

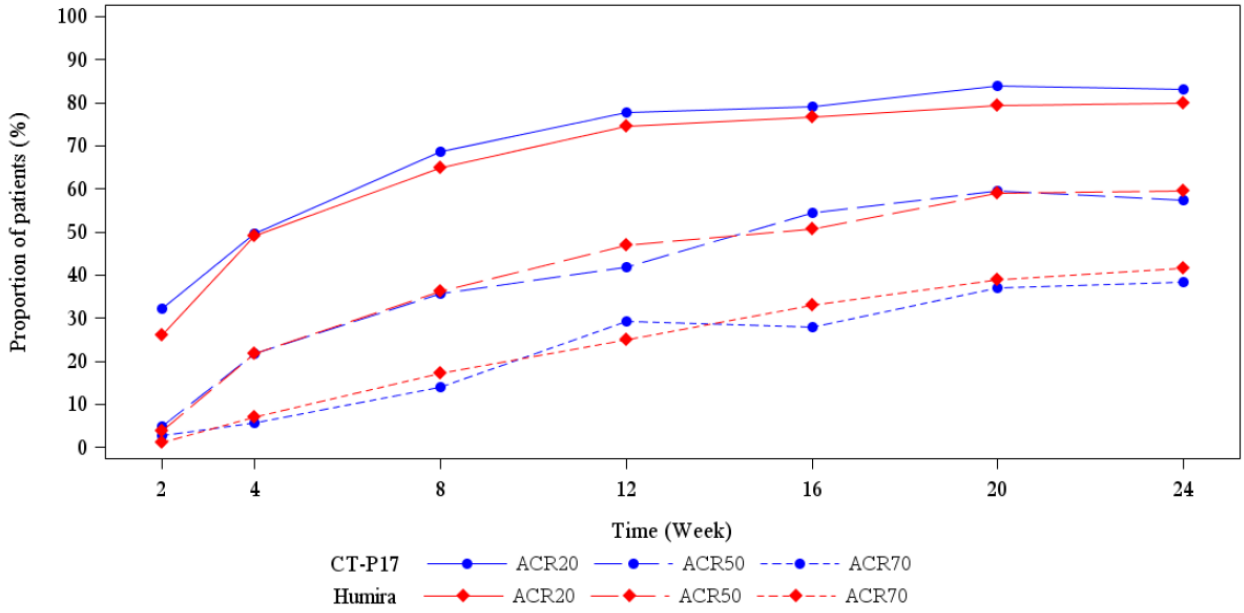
Upon CHMP's request, the applicant provided estimates of treatment difference in ACR20 at weeks 12 and 24 for the ITT and PP populations stratified by disease activity, country, geographical region, ADA status, age, sex and body mass index (BMI). Results for the additional analyses were in agreement with the initial analyses and supported the conclusion of biosimilarity.

Impact of ADA on clinical outcome

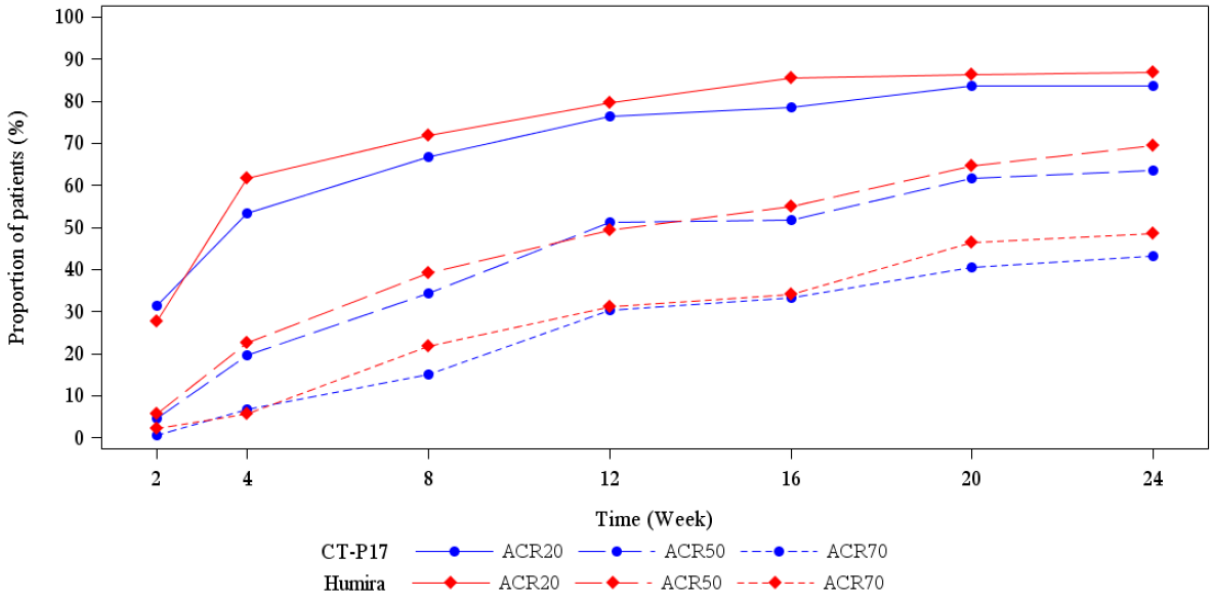
The impact of ADA on efficacy in terms of ACR20/50/70 in Treatment period I is presented graphically in Figure 7.

Figure 7 Proportion of Patients Achieving ACR20/50/70 by Post-treatment ADA Status up to Week 24:ITT Population

a) At least one ADA positive subgroup



b) All ADA negative subgroup



Upon request, the applicant provided the estimated treatment difference, including 95% CI of difference, of proportion of patients achieving response according to ACR20 by ADA status from both ITT and PP populations, from all time points. A summary of the results are provided in Table 17.

Table 17 Estimated Difference (95% CI of Difference) of Proportion of Patients Achieving Response According to ACR20 criteria by ADA Status in Study CT-P17 3.1

Visit	ADA status[1]	ACR20 Response Rate, n/N[2] (%)		Difference between CT-P17 and Humira	95% CI for the Difference
		CT-P17	EU-Humira		
ITT Population and ITT Population – Treatment Period II subset[3 4]					
Week 2	Positive	14/43 (32.6)	24/86 (27.9)	4.65	(-12.26, 21.56)
	Negative	88/278 (31.7)	62/236 (26.3)	5.38	(-2.45, 13.22)
Week 12	Positive	67/88 (76.1)	88/116 (75.9)	0.27	(-11.56, 12.10)
	Negative	179/228 (78.5)	159/202 (78.7)	-0.20	(-7.97, 7.56)
Week 24	Positive	81/93 (87.1)	95/116 (81.9)	5.20	(-4.57, 14.97)
	Negative	187/216 (86.6)	173/196 (88.3)	-1.69	(-8.09, 4.71)
Week 36	Positive	69/76 (90.8)	35/41 (85.4)	5.42	(-7.20, 18.05)
	Negative	200/222 (90.1)	102/112 (91.1)	-0.98	(-7.56, 5.60)
Week 48	Positive	80/85 (94.1)	41/45 (91.1)	3.01	(-6.70, 12.71)
	Negative	186/202 (92.1)	99/105 (94.3)	-2.21	(-8.00, 3.59)
Week 52 (EOS)	Positive	80/86 (93.0)	37/42 (88.1)	4.93	(-6.25, 16.10)
	Negative	164/181 (90.6)	82/87 (94.3)	-3.65	(-10.12, 2.83)
PP Population and PP Population – Treatment Period II subset[3 5]					
Week 2	Positive	12/39 (30.8)	22/74 (29.7)	1.04	(-16.80, 18.88)
	Negative	82/246 (33.3)	53/202 (26.2)	7.10	(-1.36, 15.55)
Week 12	Positive	61/77 (79.2)	75/94 (79.8)	-0.57	(-12.73, 11.60)
	Negative	163/208 (78.4)	147/182 (80.8)	-2.40	(-10.41, 5.60)
Week 24	Positive	75/85 (88.2)	81/96 (84.4)	3.86	(-6.12, 13.84)
	Negative	173/200 (86.5)	159/180 (88.3)	-1.83	(-8.50, 4.83)
Week 36	Positive	66/72 (91.7)	31/36 (86.1)	5.56	(-7.42, 18.53)
	Negative	187/207 (90.3)	92/102 (90.2)	0.14	(-6.89, 7.18)
Week 48	Positive	76/80 (95.0)	35/39 (89.7)	5.26	(-5.40, 15.91)
	Negative	173/189 (91.5)	91/97 (93.8)	-2.28	(-8.50, 3.94)
Week 52 (EOS)	Positive	77/81 (95.1)	31/36 (86.1)	8.95	(-3.29, 21.19)
	Negative	154/170 (90.6)	78/82 (95.1)	-4.53	(-10.94, 1.87)

Note. Percentages are calculated by using the number of patients with ADA status at each visit as the denominator. The 95% CI for the difference of ACR20 response proportion between two treatment groups was calculated using asymptotic method.

Abbreviations: ACR20, American College of Rheumatology 20% improvement criteria; ADA, anti-drug antibody; EU, European Union; ITT, intent-to-treat.

[1] Anti-drug antibody status at each visit.

[2] The numerator is based on number of patients who had ADA positive or ADA negative results at each visit. The denominator is based on number of patients who had immunogenicity results at each visit.

[3] For Treatment Period II, the results, 95% CI for difference were based on CT-P17 maintenance and Humira maintenance groups.

[4] 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.

[5] 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.

In Treatment period 1 (up to week 24), ADA positive patients gained slightly better response rates with CT-P17 treatment than with Humira, while ADA negative patients gained slightly better response rates with Humira. The differences were small and not clinically significant in either of the study populations (ITT and PP) and at all time points.

From week 26 onward, the mean differences between treatment arms grew slightly bigger, in particular among ADA positive patients. At most, there was a difference of 12.8 percentage points in ACR20 response rate among ADA positive patients between CT-P17 maintenance treatment and Humira maintenance treatment at week 26 in the ITT population. Confidence intervals were broad throughout treatment period II and while all the 95% CIs contained 0, the upper limit of the 95% CIs was continuously above 15% among ADA positive patients in both study populations (Table 18).

Among ADA negative patients differences between treatment arms in ACR20 response were small, ranging from -4.5 to 2.3 percentage points and with 95% CIs falling within the +/- 15% range.

Table 18 Truncated summary of ACR20 by visit based ADA status ITT Population - Treatment Period II Subset

Visit ADA Status	CT-P17 Maintenance (N=303)	Humira Maintenance (N=153)	Switched to CT-P17 (N=152)	Difference between CT-P17 Maintanence and Humira Maintenance	95% CI for the Difference
Week 26					
Positive	67/74 (90.5%)	35/45 (77.8%)	47/51 (92.2%)	12.76	(-1.09, 26.62)
Negative	204/229 (89.1%)	96/108 (88.9%)	94/101 (93.1%)	0.19	(-6.98, 7.37)
Week 28					
Positive	66/75 (88.0%)	37/46 (80.4%)	41/45 (91.1%)	7.57	(-6.05, 21.19)
Negative	207/226 (91.6%)	94/106 (88.7%)	98/105 (93.3%)	2.91	(-4.12, 9.95)
Week 32					
Positive	69/76 (90.8%)	35/42 (83.3%)	41/45 (91.1%)	7.46	(-5.56, 20.47)
Negative	204/224 (91.1%)	103/111 (92.8%)	98/106 (92.5%)	-1.72	(-7.81, 4.37)
Week 36					
Positive	69/76 (90.8%)	35/41 (85.4%)	37/41 (90.2%)	5.42	(-7.20, 18.05)
Negative	200/222 (90.1%)	102/112 (91.1%)	104/109 (95.4%)	-0.98	(-7.56, 5.60)
Week 40					
Positive	77/82 (93.9%)	39/46 (84.8%)	38/42 (90.5%)	9.12	(-2.48, 20.72)
Negative	195/215 (90.7%)	100/107 (93.5%)	104/106 (98.1%)	-2.76	(-8.85, 3.32)
Week 44					
Positive	78/85 (91.8%)	39/45 (86.7%)	41/45 (91.1%)	5.10	(-6.43, 16.62)
Negative	193/212 (91.0%)	96/105 (91.4%)	97/101 (96.0%)	-0.39	(-6.98, 6.20)

Abbreviation: ADA = Anti-drug Antibody.

Note: Percentages are calculated by using the number of patients with ADA status at each visit as the denominator. The 95% CI for the difference of ACR20 response proportion between two treatment groups was calculated using asymptotic method.

The impact of immunogenicity on efficacy was also assessed by ADA titre in treatment period I and the analyses showed that, while higher ADA titre correlated with lower drug exposure, obvious correlation between immunogenicity and efficacy was not found in either of the treatment arms.

Usability of PFS (CT-P17 3.1)

The applicant has conducted usability assessments concerning PFS as part of study 3.1 using PRE- and POST-SIAQ questionnaire (patient rating) and Self-Injection Assessment Checklist (observer rating). Usability assessments were performed only for patients who self-injected the study drug (Bulgaria and Poland only). Altogether, 146 patients agreed to participate in the usability assessment (out of the 501 patients in Poland and Bulgaria), 70 in CT-P17 group and 76 in EU-Humira group, respectively. Usability assessments were conducted at Weeks 4, 6, 8 and 24.

According to the applicant's analyses, all patients rated self-injection with mean PRE- and POST-SIAQ scores over 7 on all domains of the SIAQ at Weeks 4, 6, 8 and 24, with the exception of self-confidence, which ranged from mean score of 5 to 6. All patients were able to successfully complete, not only the critical tasks (N7, N10, N11 and N12), but also 14 instructions from the Self-Injection Assessment Checklist for both treatment groups of the usability population throughout all usability assessment periods up to Week 24.

Some bias toward overly optimistic results might have occurred at week 4 due to training too close to the usability assessment and possibly due to patient selection. However, results are similar for both CT-P17 and Humira and the overall usability of CT-P17 PFS is satisfactory.

Summary of main study

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

Table 19 Summary of Efficacy for trial CT-P17 3.1

<table>
<tr><td colspan="3">Title: A Randomised, 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</td></tr>
<tr><td>Study identifier</td><td colspan="2">CT-P17 3.1</td></tr>
<tr><td rowspan="2">Design</td><td colspan="2">This study was a randomised, active-controlled, double-blind, multicentre, Phase 3 study. A total of 648 patients with moderate to severe active RA were randomised in a 1:1 ratio to receive multiple single-dose (40mg) of either CT-P17 40 mg (N=324) or EU-Humira (N=324) administered by subcutaneous (SC) injection via pre-filled syringe (PFS) every other week (EOW) for 48 weeks. The study period for up to 52 weeks after 1st randomisation includes 48 weeks of treatment and 4 weeks of safety follow-up. Prior to dosing at Week 26, all patients underwent the 2nd randomisation process. Patients who were initially randomly assigned to EU-Humira were randomised again in a ratio of 1:1 to either continue EU-Humira or undergo transition to CT-P17. The primary endpoint is the proportion of patients achieving clinical response according to the ACR criteria at Week 24. Secondary endpoints are to evaluate additional efficacy, PK, PD, usability and overall safety including immunogenicity and biomarker over 52 weeks.</td></tr>
<tr><td>Duration of main phase:

Duration of Run-in phase:
Duration of Extension phase:</td><td>24 weeks (primary endpoint), 48 weeks (end of active treatment)
Not applicable
Not applicable</td></tr>
</table>

Hypothesis	Equivalence margin of the difference in ACR20 response rate at Week 24 [-15%, 15%]		
Treatments groups	CT-P17	40 mg SC, EOW, up to Week 24, 324 patients randomised.	
	EU-Humira	40 mg SC, EOW, up to Week 24, 324 patients randomised.	
	CT-P17 Maintenance	40 mg SC, EOW, from Week 26 to Week 48, 303 patients randomised.	
	EU-Humira Maintenance	40 mg SC, EOW, from Week 26 to Week 48, 153 patients randomised.	
	Switched to CT-P17	40 mg SC, EOW, from Week 26 to Week 48, 152 patients randomised.	
Endpoints and definitions	Primary endpoint	ACR20	ACR20 response rate at Week 24
	Secondary Efficacy endpoints	ACR20	ACR20 (except for Week 24) response rate over 52 weeks
		ACR50	ACR50 response rate over 52 weeks
		ACR70	ACR70 response rate over 52 weeks
		Hybrid ACR response	Combined ACR20, ACR50, ACR70 and continuous score of the mean improvement in core set measures over 52 weeks.
		DAS28	Actual value and change from baseline in DAS28 (CRP), DAS28 (ESR) over 52 weeks.
		EULAR response	The European League Against Rheumatism (EULAR) response over 52 weeks.
		CDAI and SDAI	Clinical disease activity index (CDAI) and Simplified disease activity index (SDAI) over 52 weeks.
Database lock	Interim Database lock (19 December 2019) for data up to Week 24. Final Database lock (25 June 2020) for data up to Week 52.		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent-to-treat (ITT) population Per-protocol (PP) population Week 24		
Descriptive statistics and estimate variability	Treatment group	CT-P17	EU-Humira
	Number of subject	ITT: 324 PP: 285	ITT: 324 PP: 276
	ACR20 response rate (ITT)	268/324 (82.72%)	268/324 (82.72%)
	ACR20 response rate (PP)	248/285 (87.02%)	240/276 (86.96%)
Effect estimate per comparison	ACR20 response rate (ITT)	Comparison groups	CT-P17 vs. EU-Humira
		Treatment difference estimate (%)	0.00
		95% CI (%)	(-5.94, 5.94)
		Equivalence margin (%)	[-15, 15]

	ACR20 response rate (PP)	Comparison groups	CT-P17 vs. EU-Humira	
		Treatment difference estimate (%)	0.06	
		95% CI (%)	(5.60, 5.78)	
		Equivalence margin (%)	[-15, 15]	
Analysis description	**Secondary Analysis**			
Analysis population and time point description	Intent-to-treat (ITT) population – Treatment Period II subset, Week 52			
Descriptive statistics and estimate variability	Treatment group	CT-P17 Maintenance	EU-Humira Maintenance	Switched to CT-P17
	Number of subject	303	153	152
	ACR20 response rate	244 (80.5%)	119 (77.8%)	125 (82.2%)
	ACR50 response rate	201 (66.3%)	95 (62.1%)	101 (66.4%)
	ACR70 response rate	135 (44.6%)	75 (49.0%)	72 (47.4%)
	Hybrid ACR (SD)	64.542 (22.2846)	67.039 (22.4088)	65.472 (26.0275)
	DAS28 (CRP) mean change (SD)	-2.945 (1.1273)	-3.074 (1.1926)	-2.983 (1.2529)
	EULAR response (CRP) No response Moderate response Good response	 6 (2.0%) 63 (20.8%) 195 (64.4%)	 4 (2.6%) 28 (18.3%) 97 (63.4%)	 9 (5.9%) 28 (18.4%) 97 (63.8%)
	CDAI mean change (SD)	-30.980 (11.5170)	-31.549 (11.4058)	-31.152 (13.5302)
	SDAI mean change (SD)	-31.235 (11.6048)	-31.935 (11.6042)	-31.747 (13.8054)
Effect estimate per comparison	ACR20 response rate	Comparison groups	CT-P17 Maintenance and Humira Maintenance	
		Treatment difference estimate (%)	2.75	
		95% CI (%)	(-4.99, 11.19)	
	ACR50 response rate	Comparison groups	CT-P17 Maintenance and Humira Maintenance	
		Treatment difference estimate (%)	4.25	
		95% CI (%)	(-5.08, 13.81)	
	ACR70 response rate	Comparison groups	CT-P17 Maintenance and Humira Maintenance	
		Treatment difference estimate (%)	-4.47	
		95% CI (%)	(-14.24, 5.35)	
	DAS28 (CRP)	Comparison groups	CT-P17 Maintenance and Humira Maintenance	

		Treatment difference estimate (%)	0.12
		95% CI (%)	(-0.12, 0.36)
Notes	No statistical comparison was planned for secondary endpoints. For ACR20, ACR50, ACR70, DAS28(CRP), statistical comparisons were performed as post-hoc. Sensitivity analysis on primary efficacy endpoint using logistic regression confirmed the results.		

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

Not applicable.

Clinical studies in special populations

Not applicable.

2.4.2. Supportive study

The usability of the AI has been studied in human factor (HF) studies (one formative HF study and one HF validation study). In addition, usability of AI has been studied in the clinical study CT-P17 3.2.

HF validation study

The applicant has conducted a HF validation study with the AI including adult RA patients (n=30), adolescent JIA patients (n=15), lay caregivers (n=30) and healthcare professionals (n=15). In total, 50% of the RA patients and lay caregivers were considered to be injection-naïve. According to the obtained results, altogether 19% (17/90) of participants did not manage to deliver a full dose during the first attempt (Instruction for use (IFU) optional). Sixteen (16) participants prematurely removed the injection device from the injection pad (before 2nd click) mainly due to neglecting IFU and relying on previous experience with other devices. Altogether, 16 out of these 17 delivered a full dose on the second injection simulation (IFU mandatory).

It was noted that there were some limitations in the HF report and for example, the observed Use Errors/Use Difficulties in most important IFU steps were not adequately discussed in the report. According to the report, only a few complaints were recorded concerning device interface. Despite the limitations, the root analyses of the study report provide evidence on safe AI usability.

Study CT-P17 3.2

The applicant has conducted a phase III, open-label, single-arm, multiple-dose study to evaluate usability of subcutaneous AI of CT-P17 in patients with moderate to severe active RA.

Altogether, 62 RA patients (mean 50.9, range 19-70 years) were analysed in terms of usability (usability population = ITT). Study population consisted of 20 males and 42 females, all whites. A majority of patients (41 patients) were classified to have ACR functional status class II, 17 had ACR functional class I and 4 had class III functional ability. According to the applicant, there were no major protocol deviations.

The primary usability endpoint was the patient's rating of PRE- and POST-SIAQ at Week 4. All patients in the usability and ITT populations rated self-injection with mean scores above 8 for pre- and post- injections on all domains of the SIAQ at Week 4 except for the domain of self-confidence.

The secondary usability endpoints were patient's rating of PRE- and POST-SIAQ at Weeks 0, 2, and 24, and the observer's rating of successful self-injection using self-injection assessment checklist at Weeks 0, 2, 4, and 24. All patients rated self-injection with mean scores over 6 for pre- and post- injection on all domains of the SIAQ at Weeks 0 and 2 in the usability and ITT populations except for the domain of self-confidence of PRE-SIAQ at Week 0. At Week 24, all patients rated self-injection with mean scores over 8 for pre- and post-injection on all domains of the SIAQ except for the domain of self-confidence.

Scores related to post-injection were generally higher than those of pre-injection. There was an increasing trend found in both pre- and post-injection scores over time.

According to the applicant, all patients successfully administered the whole volume of medication at weeks 0, 2, 4 and 24 and all patients completed all necessary use tasks (self-injection assessment checklist) at all time points. The study CT-P17 3.2 was designed to assess usability based on a single trial of injection. A majority of patients successfully performed self-injection at the first attempt. However, three patients failed to inject the whole volume on first attempt. All of these patients self-injected successfully after further instructions during the same visit. The applicant decided to record these incidences as successful. This approach is not acceptable to the CHMP as it obscures the results and defies the purpose of the study. However, as there were only three incidences of misrecording, the general conclusion of sufficient usability of the AI device is not affected.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study CT-P17 3.1 was the comparative study for assessment of similarity of clinical efficacy and safety between CT-P17 and the originator EU-Humira. It was a phase 3, randomised, active-controlled, double-blind, multicentre study designed to evaluate efficacy, PK, PD, usability, overall safety and immunogenicity of multiple single-doses (40 mg) of either CT-P17 or EU-Humira administered by SC injection via PFS in combination with MTX in patients with moderate to severe active RA. The design of the study is considered adequate to the CHMP and in line with the EMA guideline on assessment of biosimilarity (EMA/CHMP/BMWP/403543/2010).

RA has been extensively used in applications for adalimumab biosimilars and RA is considered a sufficiently sensitive target population. The selection criteria ensured inclusion of a representative target population and known safety concerns were taken into account in the exclusion criteria.

The primary objective of this study was to demonstrate that CT-P17 is equivalent to EU-approved Humira as determined by clinical response according ACR20 at Week 24. The primary endpoint of study CT-P17 3.1 was the proportion of patients achieving clinical response according to the ACR20 at Week 24 in the ITT population. ACR20 is considered an acceptable primary endpoint in the EMA Guideline on clinical investigation of medicinal products for the treatment of RA and it has been widely used in equivalence trials. However, while ACR20 at 6 months is adequate for assessment of efficacy in non-inferiority trials, an earlier time point, before the therapeutic plateau is fully developed, is preferred in equivalence trials, to increase the sensitivity to detect possible differences. In addition to the primary efficacy endpoint of ACR20 response at week 24,

the totality of data, including ACR20 response at all time points, is thus considered important for the assessment of equivalence on clinical efficacy.

The predefined equivalence margin of -15% to 15% was not justified in the study protocol, as advised in the EMA Guideline on the choice of the non-inferiority margin. According to the Summary of Clinical efficacy, written after data analysis, the delta was chosen to preserve 50% of the effect of adalimumab over placebo seen in two historical meta-analyses. The equivalence margin (EM) of -15% to 15% is in line with several previous adalimumab biosimilar processes and is acceptable to the CHMP. Upon request, the applicant clarified that the justification of the predefined EM was in place before the start of the study. Non-responder imputation method was used in the ITT population analyses of ACR response rates. However, in an equivalence trial, use of the full analysis set with non-responder imputation is generally not conservative. In equivalence trials the PP population is considered more conservative and the preferred population of analysis, as stated in the ICH E9 Statistical Principles for Clinical Trials. Hence, the results for the PP population are considered even more relevant than the results for the primary ITT population.

The secondary endpoints (ACR50, ACR70, hybrid ACR response, DAS28, EULAR response, CDAI, SDAI, quality of life [SF-36]) are validated and in line with what has been used in previous applications with RA indications.

The 48-week treatment duration is considered by the CHMP sufficient to assess persistence of response and in line with the EMA guideline (CPMP/EWP/556/95 Rev. 2). Of note, only data up to week 24 was initially submitted. The full study report was provided during the procedure. Overall, the conduct of the study was adequate to the CHMP. There was no GCP inspection conducted by local regulatory authorities and no specific GCP issues arose during assessment. However, some clarification was requested to confirm that planning of the statistical analysis and reporting of the usability results were prudent. All issues were resolved upon satisfactory clarification.

The usability of the AI and PFS was studied in the studies (CT-P17 3.1, CT-P17 3.2 and a HF study). Usability assessment in Studies CT-P17 3.1 and 3.2 with RA patients using PRE- and POST- modules of SIAQ and Self-Injection Assessment Checklist showed that CT-P17 PFS and AI devices can be used and self-injected safely to deliver the medicinal product to the target population.

Efficacy data and additional analyses

In total, 648 patients with moderate to severe active RA were randomised and initiated treatment. The study population was representative of RA patients in general and the treatment groups were well balanced in terms of basic demographic characteristics, disease duration, disease severity and use of concomitant medication.

In both treatment arms, 82.72% of patients in the ITT population achieved response according to ACR20 at week 24 (primary efficacy endpoint). The response rates are comparable to those seen in previous trials with Humira. The 95% CI for the estimate of treatment difference in ACR20 response rates at week 24 was entirely within the predefined equivalence margin of -15% to 15% for both ITT and PP populations. The results were unchanged after controlling for country and disease activity. Hence, the primary objective of this trial was met and the result was unchanged by sensitivity analysis. However, as stated above, week 24 is not the most sensitive time point for assessing equivalence of efficacy in RA and therefore the totality of data, including response per each visit is important.

As the PP population is considered more conservative in equivalence trials, the results for the PP population are considered even more relevant than the results for the primary ITT population.

Upon CHMP's request, the applicant provided during the evaluation confidence intervals for the estimate of treatment difference in ACR20, ACR50, and ACR70 at all time points up to the EOS for both ITT and PP populations. Estimates of difference between treatment arms were small and most of the 95% CIs remained within +/- 15% in both the ITT and the PP populations at all time points up to week 52. Data from the most sensitive time points (weeks 8-16) and from the more sensitive population of analysis (PP) confirmed similarity in efficacy according to ACR criteria between CT-P17 and Humira. Similar efficacy was maintained also after switching to CT-P17 at week 26 and up to week 52. Similarity was also supported by results on the continuous DAS28 scale. The data showed high similarity between treatment arms in actual values and change from baseline of the DAS28(CRP) and DAS28(ESR) scores, over time, across different visit time points in both ITT and PP populations. The difference between the mean changes from baseline in DAS28(CRP) at different visit time points were marginal and the point estimates do not exceed the difference of 0.6 in DAS28(CRP) score, generally approved to be the minimal difference of clinical importance. Moreover, the 95% CI for the estimate of treatment difference in DAS28(CRP) was entirely within the margin of clinical significance ±0.6% in both the ITT and the PP populations at all time points up to week 52.

The mean decreases from baseline in RF, anti-CCP, CRP, and ESR were comparable between the two treatment groups. Since the main efficacy endpoints were highly similar, the small differences in secondary PD markers, seen after week 24, do not preclude the conclusion of similarity.

The robustness of the efficacy results was confirmed by subgroup analyses. Estimates of treatment difference in ACR20 at weeks 12 and 24 for the ITT and PP populations were provided by subgroups of clinically relevant factors, such as disease activity, country, geographical region, age, sex and body mass index (BMI). Estimates of treatment differences were mostly within +/- 10% and did not exceed 20% in any subgroup. Results from the sub-group analyses are in agreement with the initial analyses and support the conclusion of biosimilarity.

In treatment period I the proportions of patients achieving response according to ACR20 was slightly better with CT-P17 treatment in the ADA positive group and slightly better with EU-Humira treatment in the ADA negative group. This is not intuitive, since the drug concentrations were slightly higher (~10%) in the CT-P17 arm among ADA negative patients. In treatment period II, the difference in ACR20 was enhanced among ADA positive patients, in favour of CT-P17. As the treatment groups were smaller in treatment period II, no statistically significant difference in efficacy was reached between treatment arms even among ADA positive patients, but the 95% CIs were broad and fell outside the predefined equivalence margin of +/- 15%. The point estimates of treatment difference ranged between 3.0 and 12.8 percentage points difference in ACR20 response among ADA positive patients in the ITT population in treatment period II, being most pronounced at week 26.

Interpretation of the results is complicated by the fact that ADA status is a post randomisation event and, hence, the benefits of randomisation to the interpretation of the results are not maintained. The applicant was asked to analyse these results in more detail with focus on factors that may confound interpretation of the results to better understand whether the difference in response rates in treatment period II is a factor of ADA positivity (including ADA titres and drug concentrations) or whether there is a prognostic factor that impacts development of ADAs and through that the response status.

In its response, the applicant pointed out that the efficacy assessment at week 26 is a reflection of the effect achieved by the week 24 dose, i.e. before second randomisation. Therefore, it does not seem sensible to

assess efficacy in the Humira/Humira and the Humira/CT-P17 arms separately at week 26. It was concluded that the proportion of ADA positive patients who achieved ACR20 at week 26 is very similar in the CT-P17 Maintenance arm 67 (90.5%) and in the Switched to CT-P17 arm 47 (92.2%). Since treatments were identical in the Humira maintenance arm and Switched to CT-P17 arm up to week 24, the lower proportion of patients achieving ACR20 in the Humira maintenance arm 35 (77.8%) compared to the Switched to CT-P17 arm at week 26 must be a chance finding. It follows that the continued difference between the Humira maintenance arm and CT-P17 Maintenance arm up to week 52 is also best explained by chance. The broad confidence intervals previously commented on are partly explained by small patient numbers in treatment period II.

The conclusion that the difference in response rates may be mainly attributed to the fact that more responders were assigned to the Switched to CT-P17 group than to the Humira group is supported by the fact that no significant difference was seen between ADA incidence or ADA titres between treatment groups. Moreover, the difference in efficacy as measured by ACR20 was not confirmed by any clinically significant differences in DAS28.

Overall, it is concluded by the CHMP that the small differences in ADA formation between study arms did not translate into significant differences in efficacy.

2.4.4. Conclusions on the clinical efficacy

The data from Study CT-P17 3.1 showed similarity between CT-P17 and Humira in both primary and secondary efficacy endpoints at Week 24. Similarity in efficacy was also supported by non-clinical PD data and was not significantly affected by antibody formation. Data from the second treatment period (Week 24 to 48) showed that efficacy was sustained up to week 52 in a comparable manner in all three treatment arms: CT-P17 and Humira maintenance groups as well as in patients who switched to CT-P17 at week 26. From the efficacy point of view, the claim for the biosimilarity between Yuflyma and Humira-EU is supported.

2.5. Clinical safety

In clinical studies with CT-P17 (Studies CT-P17 1.1, 1.2, 1.3 and 3.1), all analyses of safety were conducted on the safety population, which consists of all subjects who received at least one dose (full or partial) of either of the study drug. Safety assessments for the four clinical studies are as follows: AEs, serious AEs (SAEs), AEs of special interest (AESIs), immunogenicity, hypersensitivity monitoring, vital signs, weight measurements, electrocardiograms (ECGs), physical examinations, interferon-γ release assays (IGRA), chest X-rays, clinical laboratory tests, local site pains using 100 mm visual analogue scale (VAS), signs and symptoms of tuberculosis (TB).

Patient exposure

The applicant's biosimilar development programme for CT-P17 included clinical safety data from 1,166 subjects in 4 clinical studies (488 healthy male and female subjects [up to Day 71 in studies CT-P17 1.1 and 1.3], 30 healthy male subjects [up to Day 120 in study CT-P17 1.2] and 648 RA patients [up to Week 52 in study CT-P17 3.1]) who were exposed to at least one dose (full or partial) of CT-P17, EU-Humira or US-Humira. Of these, 297 healthy subjects and 324 RA patients were exposed to CT-P17 (Table 20).

Table 20 Number of subjects who received at least one dose of study drug (CT-P17 or reference products) in the studies CT-P17 1.1, 1.2, 1.3 and 3.1 (Safety population)

Study	Subjects	CT-P17 PFS 40 mg/0.4 ml	CT-P17 AI 40 mg/0.4 ml	EU-Humira PFS 40 mg/0.4 ml	US-Humira PFS 40 mg/0.4 ml	Total
	Overall Exposure – Number of Subjects					
CT-P17 1.1	Male and Female HV	102	-	104	102	308
CT-P17 1.2	Male HV	15	-	15	-	30
CT-P17 1.3	Male and Female HV	87	93	-	-	180
CT-P17 3.1	RA Patients	324	-	324	-	648
Total		621		443	102	1166

To assess biosimilarity between the proposed biosimilar CT-P17 and the reference product Humira, the applicant's clinical development programme included one pivotal Phase III confirmatory efficacy and safety study (CT-P17 3.1) in patients with RA. For details on the study population, see section 2.4. Clinical efficacy. From the safety point of view, the objective of this study was to evaluate overall safety, including immunogenicity over 52 weeks.

In addition to the pivotal biosimilarity study, safety data is also available from three Phase I single-dose studies in healthy volunteers: CT-P17 1.1 (PK study for biosimilarity), CT-P17 1.2 (safety and PK pilot study), and CT-P17 1.3 (PK study comparing AI and PFS). The safety results from these studies are considered supportive.

The applicant's development program also included an AI usability study (CT-P17 3.2) in 62 patients with RA. In this study, CT-P17 AI was administered 40 mg every other week for 24 weeks. At 24 weeks, 60 of 62 patients had successfully received all the CT-P17 doses. Only the usability results up to 4 weeks were included in the applicant's initial submission. The safety data were submitted upon CHMP's request during the procedure.

The dosing of both CT-P17 and Humira used in the presented studies corresponds to the recommended dosing stated in the Humira SmPC.

Adverse events

Overview of Adverse Events in studies CT-P17 1.1, 1.2 and 1.3, and in Treatment Period I of study CT-P17 3.1

The key safety findings related to the TEAEs are summarised in Table 21.

Table 21 Overview of TEAEs in studies CT-P17 1.1, 1.2 and 1.3, and in Treatment Period I of study CT-P17 3.1 (Safety Population)

	Study CT-P17 1.1			Study CT-P17 1.2		Study CT-P17 1.3		Study CT-P17 3.1	
	CT-P17 (N=102)	EU-Humira (N=104)	US-Humira (N=102)	CT-P17 (N=15)	EU-Humira (N=15)	CT-P17 AI (N=93)	CT-P17 PFS (N=87)	CT-P17 (N=324)	EU-Humira (N=324)
Total number of TEAEs	137	138	116	19	14	128	95	457	461
Number (%) of subjects with ≥1 TEAE	56 (54.9)	60 (57.7)	65 (63.7)	10 (66.7)	8 (53.3)	56 (60.2)	45 (51.7)	169 (52.2)	184 (56.8)
Number (%) of subjects with ≥1 Related TEAE	45 (44.1)	49 (47.1)	49 (48.0)	5 (33.3)	4 (26.7)	47 (50.5)	38 (43.7)	88 (27.2)	99 (30.6)
Number (%) of subjects with ≥1 TEAE leading to death	0	0	0	0	0	0	0	0	0
Number (%) of subjects with ≥1 TESAE	2 (2.0)	1 (1.0)	0	0	0	2 (2.2)	0	10 (3.1)	16 (4.9)
Number (%) of subjects with ≥1 TEAE leading to study drug discontinuation	1 (1.0)	0	0	0	0	0	0	5 (1.5)	8 (2.5)
Number (%) of subjects with ≥1 TEAE of hypersensitivity/allergic reactions	1 (1.0)	1 (1.0)	0	0	0	3 (3.2)	1 (1.1)	2 (0.6)	4 (1.2)
Number (%) of subjects with ≥1 TEAE of injection site reaction	20 (19.6)	19 (18.3)	16 (15.7)	0	1 (6.7)	8 (8.6)	6 (6.9)	16 (4.9)	22 (6.8)
Number (%) of subjects with ≥1 TEAE of infection	10 (9.8)	13 (12.5)	19 (18.6)	5 (33.3)	2 (13.3)	10 (10.8)	6 (6.9)	97 (29.9)	103 (31.8)
Number (%) of subjects with ≥1 TEAE of malignancy	0	0	0	0	0	0	0	1 (0.3)	0

Note: At each level of summarisation, subjects are counted once if they reported one or more events.

Phase III Study CT-P17 3.1 in patients with RA

Summary of Adverse Events

Treatment Period I

An overall summary of TEAEs in Treatment Period I is presented for the safety population in Table 22. Overall, 989 TEAEs were reported in 367 (56.6%) patients, 175 (59.3%) patients in the CT-P17 treatment group and 192 (59.3%) patients in the EU-Humira treatment group. The majority of TEAEs were grade 1 or grade 2 in intensity.

Table 22 Summary of Treatment-Emergent Adverse Events during Treatment Period I: Safety Population (Study CT-P17 3.1)

	CT-P17 (N=324)	Humira (N=324)	Total (N=648)
Total number of TEAEs	**492**	**497**	**989**
Number (%) of patients with at least 1 TEAE	175 (54.0)	192 (59.3)	367 (56.6)
Related to the study drug	90 (27.8)	107 (33.0)	197 (30.4)
Unrelated to the study drug	125 (38.6)	123 (38.0)	248 (38.3)
Total number of TESAEs	**14**	**20**	**34**
Number (%) of patients with at least 1 TESAE	12 (3.7)	19 (5.9)	31 (4.8)
Related to the study drug	5 (1.5)	6 (1.9)	11 (1.7)
Unrelated to the study drug	7 (2.2)	13 (4.0)	20 (3.1)
Total number of TEAEs leading to study drug discontinuation	**7**	**10**	**17**
Number (%) of patients with at least 1 TEAE leading to study drug discontinuation	7 (2.2)	10 (3.1)	17 (2.6)
Related to the study drug	2 (0.6)	5 (1.5)	7 (1.1)
Unrelated to the study drug	5 (1.5)	5 (1.5)	10 (1.5)
Total number of TEAEs classified as hypersensitivity/allergic reactions	**2**	**6**	**8**
Number (%) of patients with at least 1 TEAE classified as hypersensitivity/allergic reactions	2 (0.6)	4 (1.2)	6 (0.9)
Total number of TEAEs classified as injection site reactions	**27**	**73**	**100**
Number (%) of patients with at least 1 TEAE classified as injection site reactions	16 (4.9)	23 (7.1)	39 (6.0)
Total number of TEAEs classified as infection	**153**	**157**	**310**
Number (%) of patients with at least 1 TEAE classified as infection	101 (31.2)	112 (34.6)	213 (32.9)
Total number of TEAEs classified as malignancy	**1**	**0**	**1**
Number (%) of patients with at least 1 TEAE classified as malignancy	1 (0.3)	0	1 (0.2)
Total number of TEAEs leading to Death	0	0	0

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

Treatment Period II

An overall summary of TEAEs in Treatment Period II is presented for the safety population in

Table 23. Overall, 542 TEAEs were reported in 263 (43.3%) patients and the proportion of patients was similar among the three treatment groups (121 [39.9%], 69 [45.4%], and 73 [48.0%] patients in the CT-P17 maintenance, Humira maintenance, and switched to CT-P17 groups, respectively). The majority of TEAEs were grade 1 or grade 2 in intensity.

Table 23 Summary of Treatment-Emergent Adverse Events during Treatment Period II: Safety Population (Study CT-P17 3.1 Treatment Period II subset)

	CT-P17 Maintenance (N=303)	Humira Maintenance (N=152)	Switched to CT-P17 (N=152)	Total (N=607)
Total number of TEAEs	**246**	**162**	**134**	**542**
Number (%) of patients with at least 1 TEAE	121 (39.9) [a]	69 (45.4)	73 (48.0)	263 (43.3)
Related to the study drug	48 (15.8)	27 (17.8)	36 (23.7)	111 (18.3)
Unrelated to the study drug	91 (30.0)	53 (34.9)	47 (30.9)	191 (31.5)
Total number of TESAEs	**7**	**3**	**5**	**15**
Number (%) of patients with at least 1 TESAE	6 (2.0)	3 (2.0)	5 (3.3)	14 (2.3)
Related to the study drug	3 (1.0)	0	2 (1.3)	5 (0.8)
Unrelated to the study drug	4 (1.3)	3 (2.0)	3 (2.0)	10 (1.6)
Total number of TEAEs leading to study drug discontinuation	**3**	**2**	**5**	**10**
Number (%) of patients with at least 1 TEAE leading to study drug discontinuation	3 (1.0)	2 (1.3)	5 (3.3)	10 (1.6)
Related to the study drug	2 (0.7)	1 (0.7)	2 (1.3)	5 (0.8)
Unrelated to the study drug	1 (0.3)	1 (0.7)	3 (2.0)	5 (0.8)
Total number of TEAEs classified as hypersensitivity/allergic reactions	**4**	**4**	**0**	**8**
Number (%) of patients with at least 1 TEAE classified as hypersensitivity/allergic reactions	2 (0.7)	1 (0.7)	0	3 (0.5)
Total number of TEAEs classified as injection site reactions	**1**	**28**	**1**	**30**
Number (%) of patients with at least 1 TEAE classified as injection site reactions	1 (0.3)	4 (2.6)	1 (0.7)	6 (1.0)
Total number of TEAEs classified as infection	**72**	**60**	**38**	**170**
Number (%) of patients with at least 1 TEAE classified as infection	54 (17.8)	41 (27.0)	28 (18.4)	123 (20.3)
Total number of TEAEs classified as malignancy	**0**	**1**	**0**	**1**
Number (%) of patients with at least 1 TEAE classified as malignancy	0	1 (0.7)	0	1 (0.2)
Total number of TEAEs leading to Death	0	0	0	0

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

Overall Period

An overall summary of TEAEs in Overall Period of study CT-P17 3.1 as presented per initial and second randomisation is summarised for the safety population in Table 24.

Overall, 1,531 TEAEs were reported in 447 (69.0%) patients in the initial randomisation and 1,418 TEAEs in 416 patients in the second randomisation. The proportion of patients was similar between the CT-P17 and Humira treatment groups (218 [67.3%] and 229 [70.7%] patients, respectively), and among the CT-P17 maintenance, Humira maintenance and switched to CT-P17 groups (204 [67.3%], 105 [69.1%], and 107 [70.4%] patients, respectively). TEAEs considered by the investigator to be related to the study drug were

reported in 238 (36.7%) patients and the proportion of patients was similar between the CT-P17 and Humira treatment groups (109 [33.6%] and 129 [39.8%] patients, respectively) and among the CT-P17 maintenance, Humira maintenance and switched to CT-P17 groups (100 [33.0%], 55 [36.2%], and 64 [42.1%] patients, respectively).

Table 24 Summary of Treatment-Emergent Adverse Events: Safety Population (Study CT-P17 3.1 Overall Period)

	Initial Randomization		2nd Randomization		
	CT-P17 (N=324)	Humira (N=324)	CT-P17 Maintenance (N=303)	Humira Maintenance (N=152)	Switched to CT-P17 (N=152)
Total number of TEAEs	**738**	**793**	**673**	**364**	**381**
Number (%) of patients with at least 1 TEAE	218 (67.3)[a]	229 (70.7)	204 (67.3)[a]	105 (69.1)	107 (70.4)
Related to the study drug	109 (33.6)	129 (39.8)	100 (33.0)	55 (36.2)	64 (42.1)
Unrelated to the study drug	169 (52.2)	169 (52.2)	156 (51.5)	84 (55.3)	74 (48.7)
Total number of TESAEs	**21**	**28**	**12**	**10**	**13**
Number (%) of patients with at least 1 TESAE	17 (5.2)	27 (8.3)	10 (3.3)	10 (6.6)	12 (7.9)
Related to the study drug	7 (2.2)	8 (2.5)	4 (1.3)	3 (2.0)	3 (2.0)
Unrelated to the study drug	11 (3.4)	19 (5.9)	7 (2.3)	7 (4.6)	9 (5.9)
Total number of TEAEs leading to study drug discontinuation	**10**	**17**	**3**	**3**	**5**
Number (%) of patients with at least 1 TEAE leading to study drug discontinuation	10 (3.1)	17 (5.2)	3 (1.0)	3 (2.0)	5 (3.3)
Related to the study drug	4 (1.2)	8 (2.5)	2 (0.7)	1 (0.7)	2 (1.3)
Unrelated to the study drug	6 (1.9)	9 (2.8)	1 (0.3)	2 (1.3)	3 (2.0)
Total number of TEAEs classified as hypersensitivity/allergic reactions	**6**	**10**	**6**	**7**	**1**
Number (%) of patients with at least 1 TEAE classified as hypersensitivity/allergic reactions	3 (0.9)	5 (1.5)	3 (1.0)	2 (1.3)	1 (0.7)
Total number of TEAEs classified as injection site reactions	**28**	**102**	**25**	**63**	**37**
Number (%) of patients with at least 1 TEAE classified as injection site reactions	17 (5.2)	24 (7.4)	16 (5.3)	12 (7.9)	11 (7.2)
Total number of TEAEs classified as infection	**225**	**255**	**206**	**123**	**113**
Number (%) of patients with at least 1 TEAE classified as infection	133 (41.0)	152 (46.9)	125 (41.3)	74 (48.7)	68 (44.7)
Total number of TEAEs classified as malignancy	**1**	**1**	**0**	**1**	**0**
Number (%) of patients with at least 1 TEAE classified as malignancy	1 (0.3)	1 (0.3)	0	1 (0.7)	0
Total number of TEAEs leading to Death	0	0	0	0	0

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

[a] One patient in the CT-P17 maintenance group reported grade 1 TEAE of lung disorder which of causality was assessed as unknown by the investigator since this event occurred after EOS visit and diagnosis was not completed until the time of last report.

Most frequently reported Treatment-Emergent Adverse Events

Treatment Period I

All TEAEs reported for 3% or more of patients in either treatment group are summarised by preferred terms (PT) for the safety population in Table 25. The most frequently reported TEAEs for patients in the CT-P17 treatment group were upper respiratory tract infection (18 [5.6%] patients) followed by nasopharyngitis (17 [5.2%] patients). The most frequently reported TEAEs for patients in the EU-Humira treatment group were injection site reaction (23 [7.1%] patients) followed by upper respiratory tract infection (22 [6.8%] patients).

Table 25 Treatment-Emergent Adverse Events reported for ⩾3% of patients in either group during Treatment Period I, using Preferred Term: Safety Population (Study CT-P17 3.1)

	CT-P17 (N=324)	Humira (N=324)	Total (N=648)
Preferred Term	**Number (%) of patients**		
Upper respiratory tract infection	18 (5.6)	22 (6.8)	40 (6.2)
Injection site reaction	16 (4.9)	23 (7.1)	39 (6.0)
Nasopharyngitis	17 (5.2)	20 (6.2)	37 (5.7)
Neutropenia	14 (4.3)	17 (5.2)	31 (4.8)
Urinary tract infection	15 (4.6)	15 (4.6)	30 (4.6)
Alanine aminotransferase increased	11 (3.4)	17 (5.2)	28 (4.3)
Latent tuberculosis	12 (3.7)	15 (4.6)	27 (4.2)
Pharyngitis	12 (3.7)	10 (3.1)	22 (3.4)
Leukopenia	10 (3.1)	9 (2.8)	19 (2.9)
Aspartate aminotransferase increased	4 (1.2)	12 (3.7)	16 (2.5)

Note: The total number of TEAEs included all patient events. At each level of summarisation, a patient was counted only once if they reported 1 or more events. Preferred terms were arranged by decreasing total percentage and coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary, Version 22.0.

Treatment Period II

All TEAEs reported for 3% or more of patients in any treatment group in Treatment Period II are summarised by PT for the safety population – Treatment Period II subset in Table 26. Slightly higher proportion of patients was observed in alanine aminotransferase increased and leukopenia in the switched to CT-P17 group (7 [4.6%] patients each) compared to the CT-P17 maintenance and Humira maintenance groups. Among these patients, 2 (1.3%) patients in alanine aminotransferase increased and 4 (2.6%) patients in leukopenia have experienced the same event in Treatment Period I and was not a new occurrence after switching to CT-P17. In addition, alanine aminotransferase increased was reported in higher incidence in the Humira treatment group in Treatment Period I (11 [3.4%] patients in the CT-P17 treatment group and 17 [5.2%] patients in the Humira treatment group) and leukopenia was reported in similar incidence in Treatment Period I (10 [3.1%] patients in the CT-P17 treatment group and 9 [2.8%] patients in the Humira treatment group). Proportion of patients in the switched to CT-P17 group with TEAEs in the SOCs of both infections and infestations and hepatobiliary disorders were also not high compared to other treatment groups. The

applicant stated that this slight numerical difference in alanine aminotransferase increased and leukopenia is likely a chance finding and considered not clinically meaningful.

Table 26 Treatment-Emergent Adverse Events reported for ⩾3% of patients in either group during Treatment Period II, using Preferred Term: Safety Population (Study CT-P17 3.1 Treatment Period II subset)

	CT-P17 Maintenance (N=303)	Humira Maintenance (N=152)	Switched to CT-P17 (N=152)	Total (N=607)
Preferred Term	**Number (%) of patients**			
Neutropenia	15 (5.0)	6 (3.9)	8 (5.3)	29 (4.8)
Upper respiratory tract infection	10 (3.3)	11 (7.2)	6 (3.9)	27 (4.4)
Urinary tract infection	9 (3.0)	5 (3.3)	3 (2.0)	17 (2.8)
Alanine aminotransferase increased	8 (2.6)	1 (0.7)	7 (4.6)	16 (2.6)
Leukopenia	8 (2.6)	0	7 (4.6)	15 (2.5)
Nasopharyngitis	6 (2.0)	5 (3.3)	3 (2.0)	14 (2.3)
Diarrhoea	2 (0.7)	3 (2.0)	5 (3.3)	10 (1.6)

Note: At each level of summarisation, a patient was counted only once if they reported 1 or more events. Preferred terms were arranged by decreasing total percentage and coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary, Version 22.0.

Overall Period

All TEAEs reported for 5% or more of patients in any treatment group in Overall Period are summarised by PT for the safety population in Table 27 27. Slightly higher proportion of patients was observed in alanine aminotransferase increased and leukopenia in the switched to CT-P17 group (15 [9.9%] and 10 [6.6%] patients, respectively) compared to the CT-P17 maintenance and Humira maintenance groups. Among the patients reported with alanine aminotransferase increased, 5 (3.3%) patients newly reported the event in Treatment Period II, 8 (5.3%) patients reported in Treatment Period I, 2 (1.3%) patients reported in both Treatment Period I and II. Among the patients reported with leukopenia, 3 (2.0%) patients newly reported the event in Treatment Period II, 3 (2.0%) patients reported in Treatment Period I, and 4 (2.6%) patients reported in both Treatment Period I and II.

Table 27 Treatment-Emergent Adverse Events reported for ⩾5% of patients in any treatment group using Preferred Term: Safety Population (Study CT-P17 3.1 Overall Period)

	Initial Randomization		2nd Randomization		
	CT-P17 (N=324)	Humira (N=324)	CT-P17 Maintenance (N=303)	Humira Maintenance (N=152)	Switched to CT-P17 (N=152)
Preferred Term	**Number (%) of patients**				
Upper respiratory tract infection	23 (7.1)	37 (11.4)	22 (7.3)	18 (11.8)	16 (10.5)
Nasopharyngitis	23 (7.1)	26 (8.0)	22 (7.3)	16 (10.5)	8 (5.3)
Neutropenia	21 (6.5)	24 (7.4)	20 (6.6)	10 (6.6)	14 (9.2)
Urinary tract infection	22 (6.8)	21 (6.5)	18 (5.9)	9 (5.9)	10 (6.6)
Injection site reaction	17 (5.2)	24 (7.4)	16 (5.3)	12 (7.9)	11 (7.2)
Alanine aminotransferase increased	17 (5.2)	22 (6.8)	15 (5.0)	6 (3.9)	15 (9.9)
Pharyngitis	16 (4.9)	17 (5.2)	15 (5.0)	9 (5.9)	8 (5.3)
Latent tuberculosis	12 (3.7)	16 (4.9)	11 (3.6)	8 (5.3)	6 (3.9)
Leukopenia	14 (4.3)	12 (3.7)	12 (4.0)	2 (1.3)	10 (6.6)
Aspartate aminotransferase increased	8 (2.5)	15 (4.6)	8 (2.6)	5 (3.3)	9 (5.9)

Note: At each level of summarisation, a patient was counted only once if they reported 1 or more events. Preferred terms was arranged by decreasing total percentage and coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary, Version 22.0.

Source: Table 12-9 in Study CT-P17 3.1 Final CSR

Treatment-Emergent Adverse Events Considered by the Investigator to be Related to the Study Drug

Treatment Period I

An overall summary of the number of patients with at least one TEAE considered by the investigator to be related to the study drug reported for ≥3% of patients in either treatment group by PT is presented for the safety population in Table 28.

In total, 90 (27.8%) patients in the CT-P17 treatment groups and 107 (33.0%) patients and the EU-Humira treatment group experienced at least one TEAE considered by the investigator to be related to the study drug. The most frequently reported TEAEs considered by the investigator to be related to the study drug in the CT-P17 treatment group were injection site reaction (16 [4.9%] patients) followed by upper respiratory tract infection (12 [3.7%] patients) and neutropenia (11 [3.4%] patients). In the EU-Humira treatment group, the most frequently reported TEAEs considered by the investigator to be related to the study drug were injection site reaction (22 [6.8%] patients) followed by neutropenia (12 [3.7%] patients) and latent tuberculosis (10 [3.1%] patients).

Table 28 Treatment-Emergent Adverse Events considered by the investigator to be related to the study drug reported for ⩾3% of patients in either group during Treatment Period I, using Preferred Term: Safety Population (Study CT-P17 3.1)

	CT-P17 (N=324)	Humira (N=324)	Total (N=648)
Preferred Term	**Number (%) of patients**		
Injection site reaction	16 (4.9)	22 (6.8)	38 (5.9)
Neutropenia	11 (3.4)	12 (3.7)	23 (3.5)
Upper respiratory tract infection	12 (3.7)	9 (2.8)	21 (3.2)
Latent tuberculosis	7 (2.2)	10 (3.1)	17 (2.6)

Note: At each level of summarisation, a patient was counted only once if they reported 1 or more events. Preferred terms was arranged by decreasing total percentage and coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary, Version 22.0.

Treatment Period II

For Treatment Period II, an overall summary of the number of patients with at least 1 TEAE considered by the investigator to be related to the study drug reported for ≥3% of patients in any treatment group by PT is summarised for the safety population – Treatment Period II subset in Table 29.

In total, 48 [15.8%], 27 [17.8%], and 36 [23.7%] patients in the CT-P17 maintenance, Humira maintenance and switched to CT-P17 groups, respectively, experienced at least one TEAE considered by the investigator to be related to the study drug.

In the CT-P17 maintenance group neutropenia (11 [3.6%] patients) was the most frequently reported, followed by leukopenia and alanine aminotransferase increased (7 [2.3%] patients each). In the Humira maintenance group, the most reported were injection site reactions and upper respiratory tract infection (4 [2.6%] patients each). In the switched to CT-P17 group, neutropenia (8 [5.3%] patients) was reported most frequently, followed by leukopenia (6 [3.9%] patients).

Table 29 Treatment-Emergent Adverse Events considered by the investigator to be related to the study drug reported for ⩾3% of patients in any treatment group during Treatment Period II, using Preferred Term: Safety Population (Study CT-P17 3.1 Treatment Period II subset)

	CT-P17 Maintenance (N=303)	Humira Maintenance (N=152)	Switched to CT-P17 (N=152)	Total (N=607)
Preferred Term	**Number (%) of patients**			
Neutropenia	11 (3.6)	3 (2.0)	8 (5.3)	22 (3.6)
Leukopenia	7 (2.3)	0	6 (3.9)	13 (2.1)
Alanine aminotransferase increased	7 (2.3)	0	5 (3.3)	12 (2.0)

Note: At each level of summarisation, a patient was counted only once if they reported 1 or more events. Preferred terms were arranged by decreasing total percentage and coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary, Version 22.0.

Overall Period

For the Overall Period, an overall summary of the number of patients with at least 1 TEAE considered by the investigator to be related to the study drug reported for ≥5% of patients in any treatment group by PT is summarised for the safety population in Table 30.

Table 30 Treatment-Emergent Adverse Events considered by the investigator to be related to the study drug reported for ⩾5% of patients in any treatment group using Preferred Term: Safety Population (Study CT-P17 3.1 Overall Period)

	Initial Randomization		2nd Randomization		
	CT-P17 (N=324)	Humira (N=324)	CT-P17 Maintenance (N=303)	Humira Maintenance (N=152)	Switched to CT-P17 (N=152)
Preferred Term	Number (%) of patients				
Injection site reaction	17 (5.2)	23 (7.1)	16 (5.3)	11 (7.2)	11 (7.2)
Neutropenia	15 (4.6)	17 (5.2)	14 (4.6)	6 (3.9)	11 (7.2)
Upper respiratory tract infection	15 (4.6)	16 (4.9)	14 (4.6)	6 (3.9)	8 (5.3)
Alanine aminotransferase increased	11 (3.4)	13 (4.0)	9 (3.0)	2 (1.3)	10 (6.6)

Treatment-Emergent Adverse Events by Intensity

Treatment Period I

Overall, 46 (7.1%) patients (16 [4.9%] patients in the CT-P17 treatment group and 30 [9.3%] patients in the EU-Humira treatment group) experienced at least one grade 3 TEAE as most severe grade and 18 (2.8%) patients (10 [3.1%] patients in the CT-P17 treatment group and 8 [2.5%] patients in the EU-Humira treatment group) experienced at least one grade 4 TEAE.

For both grade 3 and grade 4, the most frequently reported TEAE was neutropenia; grade 3 neutropenia as most severe grade was reported for 10 (1.5%) patients (4 [1.2%] patients in the CT-P17 treatment group and 6 [1.9%] patients in the EU-Humira treatment group) and grade 4 neutropenia as most severe grade was reported for 12 (1.9%) patients (6 [1.9%] patients each in the CT-P17 and EU-Humira treatment groups, respectively).

Treatment Period II

Overall, 36 (5.9%) patients (17 [5.6%], 7 [4.6%], and 12 [7.9%] patients in the CT-P17 maintenance, Humira maintenance and switched to CT-P17 groups, respectively) experienced at least 1 grade 3 TEAE and 6 (1.0%) patients (4 [1.3%], 1 [0.7%], and 1 [0.7%] patients in the CT-P17 maintenance, Humira maintenance and switched to CT-P17 groups, respectively) experienced at least 1 grade 4 TEAE. For both grade 3 and grade 4, the most frequently reported TEAE was neutropenia; grade 3 neutropenia was reported for 13 (2.1%) patients (9 [3.0%], 1 [0.7%], and 3 [2.0%] patients in the CT-P17 maintenance, Humira maintenance and switched to CT-P17 groups, respectively) and grade 4 neutropenia was reported for 2 (0.7%) patients in the CT-P17 maintenance and none in the Humira maintenance and switched to CT-P17 groups.

Overall Period

The majority of TEAEs were Common terminology criteria for adverse events (CTCAE) grade 1 or grade 2 in intensity. No grade 5 TEAEs were reported in any treatment group. Overall, 70 (10.8%) patients (29 [9.0%] and 41 [12.7%] patients in the CT-P17 and Humira treatment groups, respectively, and 24 [7.9%], 13 [8.6%], and 24 [15.8%] patients in the CT-P17 maintenance, Humira maintenance and switched to CT-P17 groups, respectively) experienced at least 1 grade 3 TEAE and 22 (3.4%) patients (12 [3.7%] and 10 [3.1%] patients in the CT-P17 and Humira treatment groups, respectively, and 10 [3.3%], 6 [3.9%], and 3 [2.0%] patients in the CT-P17 maintenance, Humira maintenance and switched to CT-P17 groups, respectively) experienced at least 1 grade 4 TEAE.

For both grade 3 and grade 4, the most frequently reported TEAE was neutropenia; grade 3 neutropenia was reported for 16 (2.5%) patients (9 [2.8%] and 7 [2.2%] patients in the CT-P17 and Humira treatment groups, respectively, and 9 [3.0%], 2 [1.3%], and 5 [3.3%] patients in the CT-P17 maintenance, Humira maintenance and switched to CT-P17 groups, respectively) and grade 4 neutropenia was reported for 12 (1.9%) patients (6 [1.9%] and 6 [1.9%] patients in the CT-P17 and Humira treatment groups, respectively, and 6 [2.0%], 4 [2.6%], and 2 [1.3%] patients in the CT-P17 maintenance, Humira maintenance and switched to CT-P17 groups, respectively).

Phase I studies in healthy subjects

Study CT-P17 1.1

A summary of all TEAEs experienced by ⩾5% of subjects in any treatment group in Study CT-P17 1.1 is provided in Table 31. The total number of TEAEs as well as percentage of subjects experiencing with at least one TEAE were comparable in CT-P17 and Humira groups. The same was true for the most frequently reported TEAEs by PT: Injection site reaction, Nasopharyngitis and Headache. The majority of TEAEs were grade 1 or 2 in intensity.

Table 31 Summary of TEAEs (reported for at least 5% of subjects by PT in any treatment group) by SOC and PT in Study CT-P17 1.1 (Safety Population)

SOC PT	CT-P17 (N=102)	EU-Humira (N=104)	US-Humira (N=102)	Total (N=308)
Total Number of TEAEs	137	138	116	391
Number (%) of subjects with at least 1 TEAE	56 (54.9)	60 (57.7)	65 (63.7)	181 (58.8)
General disorders and administration site conditions	23 (22.5)	23 (22.1)	18 (17.6)	64 (20.8)
Injection site reaction	20 (19.6)	19 (18.3)	16 (15.7)	55 (17.9)
Infections and infestations	10 (9.8)	13 (12.5)	19 (18.6)	42 (13.6)
Nasopharyngitis	3 (2.9)	3 (2.9)	7 (6.9)	13 (4.2)
Nervous system disorders	7 (6.9)	10 (9.6)	9 (8.8)	26 (8.4)
Headache	6 (5.9)	7 (6.7)	6 (5.9)	19 (6.2)

Note: At each level of summarisation, subjects are counted once if they reported one or more events.

Study CT-P17 1.2

In Study CT-P17 1.2, at least one TEAE was reported for 10 [66.7%] subjects in the CT-P17 treatment group and 8 [53.3%] subjects in the EU-Humira treatment group. The most frequently reported TEAE by SOC was infections and infestations: 5 [33.3%] subjects in the CT-P17 treatment group and 2 [13.3%] subjects in the EU-Humira treatment group. The proportion of subjects with TEAEs considered by the investigator to be related to the study drug was comparable between the two treatment groups. All TEAEs were grade 1 or 2 in intensity.

Study CT-P17 1.3

In Study CT-P17 1.3 comparing CT-P17 AI and CT-P17 PFS, the majority of TEAEs were grade 1 or 2 in intensity. A summary of all TEAEs experienced by ⩾5% of subjects in either treatment group is provided in Table 32. A higher percentage of subjects with TEAEs in the musculoskeletal and connective tissue disorders (system organ class (SOC)) was reported in the AI treatment group (15.1%) compared to the PFS treatment group (3.4%). However, all TEAEs in this SOC were grade 1, except 1 grade 3 TESAE case in the CT-P17 AI treatment group reported as rhabdomyolysis. TEAEs within this SOC that were reported in more than one subject in either treatment group were Musculoskeletal pain (7 subjects in AI group, 1 subject in PFS group), Arthralgia (4 vs. 0), Back pain (4 vs. 1) and Myalgia (2 vs. 0). All subjects recovered without sequelae from these TEAEs. The proportion of subjects with other TEAEs reported for at least 5% of subjects was comparable in both treatment groups.

Table 32 Summary of TEAEs (reported for at least 5% of subjects by PT in either treatment group) by SOC and PT in Study CT-P17 1.3 (Safety Population)

SOC **PT**	**CT-P17 AI (N=93)**	**CT-P17 PFS (N=87)**	**Total (N=180)**
Total Number of TEAEs	128	95	223
Number (%) of subjects with at least 1 TEAE	56 (60.2)	45 (51.7)	101 (56.1)
General disorders and administration site conditions	10 (10.8)	9 (10.3)	19 (10.6)
Injection site reaction	8 (8.6)	6 (6.9)	14 (7.8)
Investigations	18 (19.4)	14 (16.1)	32 (17.8)
Blood creatine phosphokinase increased	7 (7.5)	4 (4.6)	11 (6.1)
C-reactive protein increased	5 (5.4)	5 (5.7)	10 (5.6)
Metabolism and nutrition disorders	8 (8.6)	6 (6.9)	14 (7.8)
Dyslipidaemia	8 (8.6)	5 (5.7)	13 (7.2)
Musculoskeletal and connective tissue disorders	14 (15.1)	3 (3.4)	17 (9.4)
Musculoskeletal pain	7 (7.5)	1 (1.1)	8 (4.4)
Nervous system disorders	12 (12.9)	10 (11.5)	22 (12.2)
Headache	11 (11.8)	8 (9.2)	19 (10.6)

Note: At each level of summarisation, subjects are counted once if they reported one or more events.

AI usability study CT-P17 3.2 in patients with RA

An overall summary of AEs is presented for the safety population in Table 33. Overall, 72 TEAEs were reported for 35 (56.5%) patients in this study. The majority of TEAEs were grade 1 or grade 2 in severity.

The most frequently reported TEAE was upper respiratory tract infection (13 [21.0 %] patients), followed by urinary tract infection (3 [4.8 %] patients). Treatment-emergent AEs considered to be related to the study drug by the investigator were reported in 27 (43.5%) patients. Of these, the most frequently reported was upper respiratory tract infection, which was reported in 9 (14.5%) patients. The other TEAEs considered by the investigator to be related to the study drug reported for ≥ 3% of patients were headache, hyperbilirubinaemia, influenza like illness, injection site reaction and pharyngitis, each for 2 (3.2%) patients.

Table 33 Summary of Treatment-Emergent Adverse Events: Safety Population (Study CT-P17 3.2)

	CT-P17 (N=62) n (%)
Total number of TEAEs	**72**
Number (%) of patients with at least 1 TEAE	35 (56.5)
Related to the study drug	27 (43.5)
Unrelated to the study drug	15 (24.2)
Total number of TESAEs	**3**
Number (%) of patients with at least 1 TESAE	3 (4.8)
Related to the study drug	0
Unrelated to the study drug [a]	3 (4.8)
Total number of TEAEs leading to treatment discontinuation	**1**
Number (%) of patients with at least 1 TEAE leading to treatment discontinuation	1 (1.6)
Related to the study drug	0
Unrelated to the study drug [a]	1 (1.6)
Total number of TEAEs leading to death	**1**
Number (%) of patients with at least 1 TEAE leading to death	1 (1.6)
Related to the study drug	0
Unrelated to the study drug [a]	1 (1.6)
Total number of TEAEs classified as hypersensitivity/allergic reactions	**0**
Total number of TEAEs classified as injection-site reactions	**2**
Number (%) of patients with at least 1 TEAE classified as injection-site reactions	2 (3.2)
Total number of TEAEs classified as infection	**31**
Number (%) of patients with at least 1 TEAE classified as infection	20 (32.3)
Total number of TEAEs classified as malignancy	**0**

[a] One patient experienced a lower gastrointestinal haemorrhage which was reported as TESAE, TEAE leading to treatment discontinuation and TEAE leading to death.

Serious adverse event/deaths/other significant events

Serious adverse events

Phase III Study CT-P17 3.1 in patients with RA

Treatment Period I

All TESAEs during TP I are summarised by SOC and PT in Table 34.

Table 34 Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term: Safety Population (Study CT-P17 3.1 Treatment Period I)

System Organ Class Preferred term	CT-P17 (N=324) Number (%) of patients	Humira (N= 324)	Total (N= 648)
Total number of TESAEs	**14**	**20**	**34**
Number of patients with at least 1 TESAE	**12 (3.7)**	**19 (5.9)**	**31 (4.8)**
Related to the study drug	5 (1.5)	6 (1.9)	11 (1.7)
Unrelated to the study drug	7 (2.2)	13 (4.0)	20 (3.1)
Blood and lymphatic system disorders	**1 (0.3)**	**1 (0.3)**	**2 (0.3)**
Neutropenia - grade 4, related	1 (0.3)	1 (0.3)	2 (0.3)
Cardiac disorders	**0**	**1 (0.3)**	**1 (0.2)**
Supraventricular tachycardia - grade 3, unrelated	0	1 (0.3)	1 (0.2)
Eye disorders	**0**	**1 (0.3)**	**1 (0.2)**
Vitreous haemorrhage - grade 3, unrelated	0	1 (0.3)	1 (0.2)
Gastrointestinal disorders	**1 (0.3)**	**0**	**1 (0.2)**
Abdominal pain - grade 2, related	1 (0.3)	0	1 (0.2)
Hepatobiliary disorders	**2 (0.6)**	**0**	**2 (0.3)**
Hepatic failure - grade 4, related	1 (0.3)	0	1 (0.2)
Nonalcoholic fatty liver disease - grade 3, unrelated	1 (0.3)	0	1 (0.2)
Infections and infestations	**4 (1.2)**	**7 (2.2)**	**11 (1.7)**
Bronchitis - grade 3, unrelated	0	1 (0.3)	1 (0.2)
Cellulitis - grade 3, related	1 (0.3)	0	1 (0.2)
Chronic tonsillitis - grade 3, unrelated	0	1 (0.3)	1 (0.2)
Epididymitis - grade 3, unrelated	0	1 (0.3)	1 (0.2)
Erysipelas - grade 3, related	1 (0.3)	0	1 (0.2)
Gastroenteritis rotavirus - grade 4, related	1 (0.3)	0	1 (0.2)
Lower respiratory tract infection - grade 3, related	0	1 (0.3)	1 (0.2)
Otitis media acute - grade 3, unrelated	1 (0.3)	0	1 (0.2)

Pulmonary tuberculosis - grade 3, unrelated	0	1 (0.3)	1 (0.2)
Pyelonephritis acute - grade 3, related	0	1 (0.3)	1 (0.2)
Tuberculosis - grade 3, related	0	1 (0.3)	1 (0.2)
Injury, poisoning and procedural complications	**2 (0.6)**	**1 (0.3)**	**3 (0.5)**
Femur fracture - grade 2, unrelated	0	1 (0.3)	1 (0.2)
Injury - grade 4, unrelated	1 (0.3)	0	1 (0.2)
Skin laceration - grade 3, unrelated	1 (0.3)	0	1 (0.2)
Musculoskeletal and connective tissue disorders	**0**	**2 (0.6)**	**2 (0.3)**
Myositis - grade 2, unrelated	0	1 (0.3)	1 (0.2)
Rheumatoid arthritis - grade 2, unrelated	0	1 (0.3)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (0.6)**	**1 (0.3)**	**3 (0.5)**
Benign muscle neoplasm - grade 1, unrelated	1 (0.3)	0	1 (0.2)
Breast cancer - grade 3, unrelated	1 (0.3)	0	1 (0.2)
Uterine leiomyoma - grade 3, unrelated	0	1 (0.3)	1 (0.2)
Nervous system disorders	**1 (0.3)**	**1 (0.3)**	**2 (0.3)**
Amyotrophic lateral sclerosis - grade 2, unrelated	1 (0.3)	0	1 (0.2)
Syncope - grade 1, unrelated	0	1 (0.3)	1 (0.2)
Renal and urinary disorders	**1 (0.3)**	**0**	**1 (0.2)**
Acute kidney injury - grade 4, related	1 (0.3)	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	**0**	**1 (0.3)**	**1 (0.2)**
Rheumatoid lung - grade 1, related	0	1 (0.3)	1 (0.2)
Surgical and medical procedures	**0**	**2 (0.6)**	**2 (0.3)**
Cataract operation - grade 2, unrelated	0	1 (0.3)	1 (0.2)
Polypectomy - grade 3, unrelated	0	1 (0.3)	1 (0.2)
Vascular disorders	**0**	**1 (0.3)**	**1 (0.2)**
Hypertension - grade 3, related	0	1 (0.3)	1 (0.2)

Note: The total number of TESAE includes all patient events in the safety populations. At each level of summarisation, a patient was counted only once if they reported one or more events. Only the most severe event was counted. System organ class and preferred terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary, Version 22.0.

Treatment Period II

All TESAEs in TP II are summarised by SOC and PT for the safety population – Treatment Period II subset in Table 35.

Table 35 Treatment-Emergent Serious Adverse Events during Treatment Period II by System Organ Class and Preferred Term: Safety Population (Study CT-P17 3.1 Treatment Period II subset)

System Organ Class Preferred term	CT-P17 Maintenance (N=303)	Humira Maintenance (N=152)	Switched to CT-P17 (N=152)	Total (N=607)
	Number (%) of patients			
Total number of TESAEs	7	3	5	15
Total patients with at least 1 TESAE	**6 (2.0)**	**3 (2.0)**	**5 (3.3)**	**14 (2.3)**
Related to the study drug	3 (1.0)	0	2 (1.3)	5 (0.8)
Unrelated to the study drug	4 (1.3)	3 (2.0)	3 (2.0)	10 (1.6)
Blood and lymphatic system disorders	**1 (0.3)**	**0**	**0**	**1 (0.2)**
Neutropenia - grade 4, related	1 (0.3)	0	0	1 (0.2)
Cardiac disorders	**0**	**1 (0.7)**	**0**	**1 (0.2)**
Angina unstable - grade 3, unrelated	0	1 (0.7)	0	1 (0.2)
Eye disorders	**0**	**0**	**1 (0.7)**	**1 (0.2)**
Retinal vein thrombosis - grade 3, related	0	0	1 (0.7)	1 (0.2)
Infections and infestations	**2 (0.7)**	**0**	**1 (0.7)**	**3 (0.5)**
Breast abscess - grade 3, related	0	0	1 (0.7)	1 (0.2)
Pneumonia - grade 3, related	1 (0.3)	0	0	1 (0.2)
Pneumonia - grade 3, unrelated	1 (0.3)	0	0	1 (0.2)
Injury, poisoning and procedural complications	**2 (0.7)**	**1 (0.7)**	**0**	**3 (0.5)**
Extradural haematoma - grade 4, unrelated	0	1 (0.7)	0	1 (0.2)
Limb crushing injury - grade 3, unrelated	1 (0.3)	0	0	1 (0.2)
Tendon rupture - grade 3, unrelated	1 (0.3)	0	0	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**1 (0.7)**	**0**	**1 (0.2)**
Basal cell carcinoma - grade 2, unrelated	0	1 (0.7)	0	1 (0.2)
Nervous system disorders	**0**	**0**	**2 (1.3)**	**2 (0.3)**
Carotid artery occlusion - grade 3, unrelated	0	0	1 (0.7)	1 (0.2)
Ischaemic stroke - grade 2, unrelated	0	0	1 (0.7)	1 (0.2)
Reproductive system and breast disorders	**1 (0.3)**	**0**	**1 (0.7)**	**2 (0.3)**
Endometrial hyperplasia - grade 3, unrelated	1 (0.3)	0	0	1 (0.2)
Endometriosis - grade 3, unrelated	0	0	1 (0.7)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	**1 (0.3)**	**0**	**0**	**1 (0.2)**
Rheumatoid lung - grade 2, related	1 (0.3)	0	0	1 (0.2)

Note: The total number of TESAE includes all patient events in the safety populations. At each level of summarisation, a patient was counted only once if they reported one or more events. Only the most severe event was counted. System organ class and preferred terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary, Version 22.0.

Overall Period

In total, 49 TESAEs were reported in 44 (6.8%) patients (17 [5.2%] and 27 [8.3%] patients in the CT-P17 and Humira treatment groups, respectively, and 10 [3.3%], 10 [6.6%], and 12 [7.9%] patients in the CT-P17 maintenance, Humira maintenance, and switched to CT-P17 groups, respectively). The proportion of patients who experienced at least 1 TESAE considered by the investigator to be related to the study drug was similar among treatment groups (7 [2.2%] and 8 [2.5%] patients in the CT-P17 and Humira treatment groups, respectively, and 4 [1.3%], 3 [2.0%], and 3 [2.0%] patients in the CT-P17 maintenance, Humira maintenance, and switched to CT-P17 groups, respectively).

In conclusion, no significant differences in frequency or pattern of TESAEs were seen between treatment arms in Study CT-P17 3.1.

Phase I studies in healthy subjects

No TESAEs were reported in Study CT-P17 1.2.

In Study CT-P17 1.3, two TESAEs were reported for 2 (2.2%) subjects in the CT-P17 AI treatment group only. The two TESAEs were meningitis viral and rhabdomyolysis, which were considered by the investigator to be related to the study drug. Both were grade 3 in intensity.

- One subject experienced a TESAE of rhabdomyolysis. On the visit 56 days after administering single dose of CT-P17, the subject had several clinically significant laboratory findings including elevated CPK and CK-MB. The subject reported recent strenuous physical activity. The subject was hospitalised and recovered in 8 days without sequelae. Based on the provided narrative, the causality between study drug and rhabdomyolysis is considered unlikely in this case.
- One subject experienced a TESAE of viral meningitis. On Day 20, the subject experienced a mild headache that worsened and was constant over time with fevers as high as 39.4°C. While in the emergency room, meningitis encephalitis panel was positive for enterovirus and the subject was admitted to the hospital. The event was recovered after 12 days with treatment, and the subject completed the study.

Deaths

No death was reported during the HV studies CT-P17 1.1, 1.2 and 1.3 and the RA study CT-P17 3.1.

In the AI usability Study CT-P17 3.2 in RA patients, one death was reported. A patient who had received 4 doses of CT-P17 AI experienced lower gastrointestinal haemorrhage three days after the last dose and died due to the event on the same day. According to the investigator, this case was considered unrelated to the study drug based on medical history that included pre-existing risk factors of long-term NSAID use without gastroprotective agents, as well as heavy smoking. The investigator's judgement is endorsed based on the narrative provided by the applicant.

Adverse events of special interests

Adverse Events of Special Interest (AESIs) in the CT-P17 studies were Hypersensitivity/Allergic reactions, Injection site reactions, Infections and Malignancies. According to Humira SmPC 4.5 and EPAR of some biosimilar adalimumab medicinal products, demyelinating disease, haematological reactions, heart failure, lupus-like syndrome and liver enzyme elevations are also known to be adverse events of special interest for adalimumab. Thus, applicant was asked to provide data about their occurrence in clinical studies with CT-P17. The applicant responded that no events of demyelinating disease or lupus-like syndrome were reported

in CT-P17 studies. Moreover, in accordance with Humira SmPC 2020, subjects with a history of moderate to severe heart failure (NYHA class III or IV) were excluded from the CT-P17 studies.

Phase III Study CT-P17 3.1 in patients with RA

Hypersensitivity/Allergic reactions

Treatment Period I

A total of 2 (0.6%) patients in the CT-P17 treatment group and 4 (1.2%) in the EU-Humira treatment group experienced at least one TEAE classified as hypersensitivity/allergic reaction. The most frequently reported sign and symptom of hypersensitivity/allergic reactions was rash (including PTs of rash, rash generalised, rash macular, and rash papular) and reported in 1 (0.3%) and 3 (0.9%) patients in the CT-P17 and EU-Humira treatment groups, respectively.

All patients recovered from the event except for one patient in the EU-Humira treatment group. Two patients in the EU-Humira treatment group discontinued study treatment due to the event and one patient in the CT-P17 treatment group delayed the study drug due to the event. All TEAEs classified as hypersensitivity/allergic reactions were CTCAE grade 1 or 2 in intensity.

Treatment Period II

The number (%) of patients who experienced at least 1 TEAE classified as hypersensitivity/allergic reaction was reported for 3 (0.5%) patients (2 [0.7%] for the CT-P17 maintenance group, 1 [0.7%] for the Humira maintenance group, and none in the switched to CT-P17 group). All TEAEs classified as hypersensitivity/allergic reactions were CTCAE grade 2 in intensity. All patients recovered from the event except for two patients. One patient in the CT-P17 maintenance group who experienced grade 2 hypersensitivity (grade 2 pruritus) 2 days after Week 32 dose received oral antihistamines and was recovering at the time of last report. The patient received the study drug without interruption at Week 36 and then terminated due to patient's withdrawal from the study. The other patient was in the Humira maintenance group and experienced grade 2 hypersensitivity (grade 2 rash) 19 days after Week 48.

Overall Period

The number (%) of patients who experienced at least 1 TEAE classified as hypersensitivity/allergic reaction was reported for 8 (1.2%) patients (3 [0.9%] and 5 [1.5%] patients in the CT-P17 and Humira treatment groups, respectively, and 3 [1.0%], 2 [1.3%], and 1 [0.7%] patients in the CT-P17 maintenance, Humira maintenance, and switched to CT-P17 groups, respectively).

Injection site reactions

Treatment Period I

All TEAEs classified as injection site reactions during Treatment Period I are summarised by relationship and intensity for the safety population in Table 36.

The most frequently reported signs and symptoms of injection site reactions were injection site erythema (13 [4.0%] and 20 [6.2%] patients in the CT-P17 and EU-Humira treatment groups, respectively) followed by injection site pruritus (5 [1.5%] and 10 [3.1%] patients in the CT-P17 and EU-Humira treatment groups, respectively).

All patients recovered from the event. No action was taken with study drug for all events except for one event in one patient from the EU-Humira treatment group. This patient discontinued the study drug due to a grade 1 injection site reaction and recovered after treatment with oral antihistamine.

Table 36 Treatment-Emergent Adverse Events classified as injection site reactions by relationship and intensity during Treatment Period I: Safety Population (Study CT-P17 3.1)

System Organ Class Preferred Term	CT-P17 (N=324)	Humira (N=324)	Total (N=648)
	Number (%) of patients		
Total number of TEAEs classified as injection site reactions	**27**	**73** [a]	**100**
Number of patients with at least 1 TEAE classified as injection site reactions	**16 (4.9)**	**23 (7.1)**	**39 (6.0)**
Related	16 (4.9)	22 (6.8)	38 (5.9)
Unrelated	0	1 (0.3)	1 (0.2)
General disorders and administration site conditions	**16 (4.9)**	**23 (7.1)**	**39 (6.0)**
Injection site reaction	16 (4.9)	23 (7.1)	39 (6.0)
Related	16 (4.9)	22 (6.8)	38 (5.9)
Grade 1	12 (3.7)	17 (5.2)	29 (4.5)
Grade 2	4 (1.2)	5 (1.5)	9 (1.4)
Unrelated	0	1 (0.3) [b]	1 (0.2)
Grade 1	0	1 (0.3)	1 (0.2)

Note: The total number of TEAEs included all patient events classified as injection site reactions. At each level of summarisation, a patient was counted only once if they reported 1 or more events. Only the most severe event was counted. System organ class and preferred term were coded using MedDRA dictionary, Version 22.0.

[a] Six patients in the EU-Humira treatment group each reported more than 6 and up to 10 events of ISRs (mostly injection site erythema).

Treatment Period II

All TEAEs classified as injection site reactions in Treatment Period II are summarised by relationship and intensity for the safety population – Treatment Period II subset in Table 37. In total, the number (%) of patients who experienced at least 1 TEAE classified as injection site reaction was reported for 6 (1.0%) patients and the proportion of patients was comparable between the 3 treatment groups (1 [0.3%], 4 [2.6%], and 1 [0.7%] patients in the CT-P17 maintenance, Humira maintenance, and switched to CT-P17 groups, respectively). All TEAEs classified as injection site reactions were grade 1 or 2 in intensity. Sign and symptom of injection site reaction was injection site bruising (1 [0.3%] patient) in the CT-P17 maintenance group and injection site erythema (1 [0.7%] patient) in the switched to CTP17 group. The most frequently reported sign and symptom of injection site reactions in the Humira maintenance group was injection site erythema (4 [2.6%] patients). All patients recovered from the event. No action was taken with study drug for all events.

Table 37 Treatment-Emergent Adverse Events classified as injection site reactions by relationship and intensity during Treatment Period II: Safety Population (Study CT-P17 3.1 Treatment Period II subset)

System Organ Class Preferred Term Relationship	CT-P17 Maintenance (N=303)	Humira Maintenance (N=152)	Switched to CT-P17 (N=152)	Total (N=607)
	Number (%) of patients			
Total number of TEAEs classified as injection site reactions	**1**	**28** [a]	**1**	**30**
Number of patients with at least 1 TEAE classified as injection site reactions	**1 (0.3)**	**4 (2.6)**	**1 (0.7)**	**6 (1.0)**
Related	1 (0.3)	4 (2.6)	1 (0.7)	6 (1.0)
Unrelated	0	0	0	0
General disorders and administration site conditions	**1 (0.3)**	**4 (2.6)**	**1 (0.7)**	**6 (1.0)**
Injection site reaction	1 (0.3)	4 (2.6)	1 (0.7)	6 (1.0)
Related	1 (0.3)	4 (2.6)	1 (0.7)	6 (1.0)
Grade 1	1 (0.3)	3 (2.0)	1 (0.7)	5 (0.8)
Grade 2	0	1 (0.7)	0	1 (0.2)

Note: The total number of TEAEs included all patient events classified as injection site reactions. At each level of summarisation, a patient was counted only once if they reported 1 or more events. Only the most severe event was counted. System organ class and preferred term were coded using MedDRA dictionary, Version 22.0.

[a] Two patients in the Humira maintenance group each reported 11 and 12 events of ISRs (mostly injection site erythema).

Overall Period

In total, the number (%) of patients who experienced at least 1 TEAE classified as injection site reaction was reported for 41 (6.3%) patients and the proportion of patients was similar between the CT-P17 and Humira treatment groups (17 [5.2%] and 24 [7.4%] patients, respectively), and among the CT-P17 maintenance, Humira maintenance, and switched to CT-P17 groups (16 [5.3%], 12 [7.9%], and 11 [7.2%] patients, respectively). All TEAEs classified as injection site reactions were grade 1 or 2 in intensity.

Infections

Treatment Period I

All TEAEs classified as infection during Treatment Period I are summarised by relationship and intensity for the safety population in Table 38.

Table 38 Treatment-Emergent Adverse Events classified as infections reported for ⩾2% of patients in either group during Treatment Period I, using Preferred Term: Safety Population (Study CT-P17 3.1)

System Organ Class Preferred Term	CT-P17 (N=324)	Humira (N=324)	Total (N=648)
	Number (%) of patients		
Total number of TEAEs classified as infection	**153**	**157**	**310**
Number of patients with at least 1 TEAE classified as infection	**101 (31.2)**	**112 (34.6)**	**213 (32.9)**
Related	44 (13.6)	48 (14.8)	92 (14.2)
Unrelated	61 (18.8)	69 (21.3)	130 (20.1)
Infections and infestations	**101 (31.2)**	**112 (34.6)**	**213 (32.9)**
Upper respiratory tract infection	18 (5.6)	22 (6.8)	40 (6.2)
Nasopharyngitis	17 (5.2)	20 (6.2)	37 (5.7)
Urinary tract infection	15 (4.6)	15 (4.6)	30 (4.6)
Latent tuberculosis	12 (3.7)	15 (4.6)	27 (4.2)
Pharyngitis	12 (3.7)	10 (3.1)	22 (3.4)
Oral herpes	7 (2.2)	8 (2.5)	15 (2.3)
Bronchitis	7 (2.2)	4 (1.2)	11 (1.7)

Note: The total number of TEAEs included all patient events classified as infection. At each level of summarisation, a patient was counted only once if they reported 1 or more events. System organ class and preferred term were coded using MedDRA dictionary, Version 22.0 and preferred term was arranged by decreasing total percentage.

[a] Including PTs of urinary tract infection and urinary tract infection bacterial.

In TP I, 101 (31.2%) patients in CT-P17 and 112 (34.6%) in EU-Humira treatment group experienced at least one TEAE classified as infections. Of these, the TEAEs in 44 (13.6%) patients in the CT-P17 and 48 (14.8%) in EU-Humira treatment groups were considered by the investigator to be related to the study drug.

The most frequently reported TEAEs classified as infection for both treatment groups were nasopharyngitis and upper respiratory tract infection, both for 17 (5.2%) and 20 (6.2%) patients in the CT-P17 and EU-Humira treatment groups, respectively, followed by urinary tract infection in 15 (4.6%) and 14 (4.3%) patients in the CT-P17 and EU-Humira treatment groups, respectively, and latent tuberculosis in 12 (3.7%) and 15 (4.6%) patients in the CT-P17 and EU- approved Humira treatment groups, respectively.

The majority of TEAEs classified as infections were grade 1 or 2 in intensity. Thirteen events of grade 3 or 4 TEAEs classified as infection were reported for 11 (1.7%) patients (erysipelas, gastroenteritis rotavirus, otitis externa, otitis media, otitis media acute, and cellulitis for 4 [1.2%] patients in the CT-P17 treatment group and epididymitis, chronic tonsillitis, pulmonary tuberculosis, tuberculosis, lower respiratory tract infection, and pyelonephritis acute for 7 [2.2%] patients in the EU-approved Humira treatment group). All events except for otitis externa and otitis media occurred in 1 patient were reported as a TESAE. Most of the events were recovered without sequelae.

Treatment Period II

All TEAEs classified as infection in Treatment Period II are summarised by PT for the safety population – Treatment Period II subset in Table 39. In total, the number (%) of patients who experienced at least 1 TEAE

classified as infections was 123 (20.3%) patients (54 [17.8%] for the CT-P17 maintenance group, 41 [27.0%] for the Humira maintenance group, and 28 [18.4%] for the switched to CT-P17 group). The TEAEs classified as infection considered by the investigator to be related to the study drug were reported for 13 (4.3%), 13 (8.6%), and 16 (10.5%) patients in the CT-P17 maintenance, Humira maintenance, and switched to CT-P17 groups, respectively. The most frequently reported TEAEs for patients in the CT-P17 maintenance group were upper respiratory tract infection (10 [3.3%] patients) followed by urinary tract infection (9 [3.0%] patients) and nasopharyngitis (6 [2.0%] patients).

The most frequently reported TEAEs for patients in the Humira maintenance group were upper respiratory tract infection (11 [7.2%] patients) followed by urinary tract infection (5 [3.3%] patients) and nasopharyngitis (5 [3.3%] patients). The most frequently reported TEAEs for patients in the switched to CT-P17 group were upper respiratory tract infection (6 [3.9%] patients) followed by bronchitis (4 [2.6%] patients). The majority of TEAEs classified as infections were grade 1 or 2 in intensity.

Six events of grade 3 TEAEs classified as infection were reported for 5 (0.8%) patients (pneumonia and bronchitis for 2 [0.7%] patients in the CT-P17 maintenance group, upper respiratory tract infection and bursitis infective staphylococcal for 2 [1.3%] patients in the Humira maintenance group, and breast abscess for 1 [0.7%] patient in the switched to CT-P17 group). Pneumonia (2 patients) and breast abscess were reported as TESAEs. Most of the events were recovered without sequelae. No grade 4 TEAEs classified as infection were reported.

Table 39 Treatment-Emergent Adverse Events classified as infections reported for ⩾2% of patients in any treatment group during Treatment Period II, using Preferred Term: Safety Population (Study CT-P17 3.1 Treatment Period II subset)

System Organ Class Preferred Term	CT-P17 Maintenance (N=303)	Humira Maintenance (N=152)	Switched to CT-P17 (N=152)	Total (N=607)
	Number (%) of patients			
Total number of TEAEs classified as infection	**72**	**60**	**38**	**170**
Number of patients with at least 1 TEAE classified as infection	**54 (17.8)**	**41 (27.0)**	**28 (18.4)**	**123 (20.3)**
Related	13 (4.3)	13 (8.6)	16 (10.5)	42 (6.9)
Unrelated	41 (13.5)	29 (19.1)	14 (9.2)	84 (13.8)
Infections and infestations	**54 (17.8)**	**41 (27.0)**	**28 (18.4)**	**123 (20.3)**
Upper respiratory tract infection	10 (3.3)	11 (7.2)	6 (3.9)	27 (4.4)
Urinary tract infection	9 (3.0)	5 (3.3)	3 (2.0)	17 (2.8)
Nasopharyngitis	6 (2.0)	5 (3.3)	3 (2.0)	14 (2.3)
Pharyngitis	4 (1.3)	4 (2.6)	3 (2.0)	11 (1.8)
Bronchitis	5 (1.7)	0	4 (2.6)	9 (1.5)
Oral herpes	2 (0.7)	4 (2.6)	1 (0.7)	7 (1.2)
Tonsillitis	0	3 (2.0)	2 (1.3)	5 (0.8)

Note: The total number of TEAEs included all patient events classified as infection. At each level of summarisation, a patient was counted only once if they reported 1 or more events. System organ class and preferred term were coded using MedDRA dictionary, Version 22.0 and preferred term was arranged by decreasing total percentage.

Overall Period

In total, the number (%) of patients who experienced at least 1 TEAE classified as infections was 285 (44.0%) patients (133 [41.0%] and 152 [46.9%] patients in the CT-P17 and Humira treatment groups, respectively, and 125 [41.3%], 74 [48.7%], and 68 [44.7%] patients in the CTP17 maintenance, Humira maintenance, and switched to CT-P17 groups, respectively). The TEAEs classified as infection considered by the investigator to be related to the study drug were reported for 118 (18.2%) patients (53 [16.4%] and 65 [20.1%] patients in the CT-P17 and Humira treatment groups, respectively, and 47 [15.5%], 26 [17.1%], and 35 [23.0%] patients in the CT-P17 maintenance, Humira maintenance, and switched to CT-P17 groups, respectively).

Malignancies

During TP I, one TEAE classified as malignancy (breast cancer) was reported in one patient in the CT-P17 treatment group. In this case, lesions were found in mammography 9 days after the Week 6 dose it the study drug. The patient had family history that was considered by the investigator to be a risk factor for the event. The event was considered unrelated to study drug. This is endorsed. None of the patients in the EU-Humira treatment group reported TEAEs classified as malignancy.

During TP II, a TEAE classified as malignancy was reported in one patient in the Humira maintenance group. None of the patients in the CT-P17 maintenance and switched to CT-P17 groups reported TEAEs classified as malignancy.

Haematological reactions

Treatment Period I

Prior to Week 26, 22 [6.8%] patients in the CT-P17 treatment group and 20 [6.2%] patients in the EU-Humira treatment group reported haematological events. The most frequently reported PT was neutropenia reported for 14 [4.3%] patients in the CT-P17 treatment group and 17 [5.2%] patients in the EU-Humira treatment group. The event of neutrophil count decreased was also reported for 3 [0.9%] patients in the CT-P17 treatment group and 2 [0.6%] patients in the EU-Humira treatment group. Grade 4 events occurred in 8 [2.5%] patients in the CT-P17 treatment group and 7 [2.2%] patients in the EU-Humira treatment group, which were neutropenia reported for 6 (1.9%) patients in each treatment group and neutrophil count decreased reported for 2 (0.6%) patients in CT-P17 treatment group and 1 (0.3%) patient in EU-Humira treatment group. All grade 4 events were recovered without sequelae.

Overall Period

Up to Week 52, 30 [9.9%] patients in the CT-P17 maintenance group, 13 [8.6%] patients in the EU-Humira maintenance group, and 15 [9.9%] patients in the Switched to CT-P17 group reported haematological reactions. The most frequently reported PT was neutropenia reported for 20 [6.6%] patients in the CT-P17 maintenance group, 10 [6.6%] patients in the EU-Humira maintenance group, and 14 [9.2%] patients in the Switched to CT-P17 group. The event of neutrophil count decreased was also reported for 3 [1.0%] additional patients in the CT-P17 maintenance group, 2 [1.3%] patients in the EU-Humira maintenance group, and 1 [0.7%] patient in the Switched to CT-P17 group. Grade 4 events occurred in 8 [2.6%] patients in the CT-P17 maintenance group, 5 [3.3%] patients in the EU-Humira maintenance group, and 3 [2.0%] patient in the Switched to CT-P17 group, which were neutropenia reported for 6 (2.0%) patients in the CT-P17 maintenance group, 4 (2.6%) patients in the EU-Humira maintenance group, and 2 (1.3%) patients in the Switched to CT-P17 group and neutrophil count decreased reported for 2 (0.7%) patients in the CT-P17

maintenance group, 1 (0.7%) patient in the EU-Humira maintenance group, and 1 (0.7%) patient in the Switched to CT-P17 group. All grade 4 events were recovered without sequelae.

Liver enzyme elevations

Treatment Period I

Prior to Week 26, 41 (6.3%) patients reported liver enzyme elevations (17 [5.2%] patients in the CT-P17 treatment group and 24 [7.4%] patients in the EU-Humira treatment group). The most frequently reported PT was alanine aminotransferase increased reported for 28 (4.3%) patients (11 [3.4%] patients in the CT-P17 treatment group and 17 [5.2%] patients in the EU-Humira treatment group). Most of the events of liver enzyme elevations were grade 1 or 2 in intensity. Grade 3 or higher events occurred in 6 (0.9%) patients (2 [0.6%] patients in the CT-P17 treatment group and 4 [1.2%] patients in the EU-Humira treatment group) including 1 event of grade 4 gammaglutamyltransferase (GGT) increased. One patient in the EU-Humira treatment group experienced a grade 3 gamma GGT increased on Week 12 visit, which was upgraded to grade 4 on Week 16 visit. No treatment was reported and the event was considered as not recovered as the patient withdrew consent after Week 16 visit.

Overall Period

Up to Week 52, 51 (8.4%) patients reported liver enzyme elevations (22 [7.3%] patients in the CTP17 maintenance group, 9 [5.9%] patients in the EU-Humira maintenance group, and 20 [13.2%] patients in the Switched to CT-P17 group). In the Switched to CT-P17 group, 40 events were reported in 20 (13.2%) patients and among these events, 25 events in 13 (8.6%) patients were reported during EU-Humira administration before switching to CT-P17. The most frequently reported PT in all groups was alanine aminotransferase increased reported for 36 (5.9%) patients (15 [5.0%] patients in the CT-P17 maintenance group, 6 [3.9%] patients in the EU-Humira maintenance group, and 15 [9.9%] patients in the Switched to CT-P17 group). Most of the events of liver enzyme elevations were grade 1 or 2 in intensity. Grade 3 events occurred in 7 (1.2%) patients (3 [1.0%] patients in the CT-P17 maintenance group, none in the EU-Humira maintenance group, and 4 [2.6%] patients in the Switched to CT-P17 group). Among the 5 events of grade 3 liver enzyme elevations reported in 4 (2.6%) patients in the Switched to CT-P17 group, 3 events in 3 (2.0%) patients were reported during EU-Humira administration before switching to CT-P17. Importantly, hepatobiliary disorders system organ class also show similar proportion among the treatment groups (6 [2.0%] patients in the CT-P17 maintenance group, 4 [2.6%] patients in the EU-Humira maintenance group, and 3 [2.0%] patients in the Switched to CT-P17 group). Grade 4 events were not reported during Treatment Period II.

Phase I studies in healthy subjects

The percentages of patients with AESIs were comparable between CT-P17 and Humira groups in studies CT-P17 1.1, and 1.2, and between CT-P17 AI and PFS groups in Study CT-P17 1.3. No malignancies were reported in these studies.

Haematological reactions

In Study CT-P17 1.1, 13 (4.2%) subjects reported haematological reactions (4 [3.9%] subjects in the CT-P17 treatment group, 3 [2.9%] subjects in the EU-Humira treatment group, and 6 [5.9%] subjects in the US-Humira treatment group). The most frequently reported preferred term (PT) was neutrophil count decreased. All events of haematological reactions were grade 1 or 2 in intensity except for 1 event of grade 3 neutrophil count decreased in the US-Humira treatment group at Day 43. The concerned subject had not received any treatment for the event and the parameter recovered to normal on Day 57 visit.

In Studies CT-P17 1.2 and 1.3, no events of haematological reactions were reported.

Liver enzyme elevations

In Study CT-P17 1.1, 8 (2.6%) subjects reported liver enzyme elevations (4 [3.9%] subjects in the CT-P17 treatment group, 1 [1.0%] subject in the EU-Humira treatment group, and 3 [2.9%] subjects in the US-Humira treatment group). The most frequently reported PT was alanine aminotransferase increased. All events of liver enzyme elevations were grade 1 or 2 in intensity except for 1 event of grade 4 liver function test increased in the EU-Humira treatment group at Day29. The concerned subject had not received any treatment for this event and both parameters recovered to normal on Day 43 visit.

In Study CT-P17 1.2, no events of liver enzymes elevations were reported.

In Study CT-P17 1.3, 8 (4.4%) subjects reported liver enzyme elevations (5 [5.4%] subjects in the CT-P17 AI treatment group and 3 [3.4%] subjects in the CT-P17 PFS treatment group). The most frequently reported preferred term was alanine aminotransferase increased. All events of liver enzyme elevations were grade 1 in intensity.

AI usability study CT-P17 3.2 in patients with RA

No TEAEs classified as hypersensitivity/allergic reaction or malignancy were reported in study CT-P17 3.2. The number of patients who experienced at least 1 TEAE classified as injection-site reaction was reported for 2 (3.2%) patients. One patient experienced grade 1 TEAE classified as ISR with the symptom of injection site erythema and the other one patient experienced grade 2 TEAE classified as ISR with the symptom of injection site pain. Both events were considered by the investigator to be related to the study drug and recovered without any treatment.

The number of patients who experienced at least 1 TEAE classified as infections was 20 (32.3%) patients. The TEAEs classified as infection considered to be related to the study drug were reported for 14 (22.6%) patients. The most frequently reported TEAE classified as infection was upper respiratory tract infection in 13 (21.0%) patients, followed by urinary tract infection in 3 (4.8%) patients. The applicant states that as this study was conducted during fall and winter season, this could affect the slightly high incidence of upper respiratory tract infection. This is endorsed.

Most of TEAEs classified as infections were grade 1 or 2 in severity, with the exception of two grade 3 events (PTs of herpes zoster and tooth infection) in 2 (3.2%) patients. All TEAEs classified as infections were recovered without sequelae except for 1 (1.6%) patient with a latent TB which occurred at EOS visit.

Haematological reactions

Two (3.2%) patients reported haematological reactions, one patient with grade 2 neutropenia and the other with grade 2 leukopenia. Both patients were recovered without receiving any treatment.

Liver enzyme elevations

Two (3.2%) patients reported liver enzyme elevations, one patient with grade 1 ALT increased and the other with grade 1 transaminases increased. Both patients were recovered from the event without receiving any treatment.

Tuberculosis assessment

Phase III Study CT-P17 3.1 in patients with RA

Treatment Period I

All patients had negative IGRA result at baseline, except 1 patient. One patient had positive Interferon Gamma Release Assay (IGRA) result at screening, but was randomised in the EU-Humira treatment group by site's mistake. The patient discontinued the study treatment after the first study drug administration due to this protocol deviation.

At Week 12, 23 (3.5%) patients (10 [3.1%] patients in the CT-P17 treatment group and 13 [4.0%] patients in the EU-Humira treatment group) had positive IGRA results. At Week 24, 10 (1.5%) patients (2 [0.6%] patients in the CT-P17 treatment group and 8 [2.5%] patients in the EU-Humira treatment group) had positive IGRA results. Twenty nine (4.5%) patients (12 [3.7%] patients in the CT-P17 treatment group and 17 [5.2%] patient in the EU-Humira treatment group) had positive IGRA conversion up to Week 24. Latent TBs (defined as a positive result of IGRA with negative examination of chest X-ray) were reported in 27 (4.2%) patients (12 [3.7%] patients in the CT-P17 treatment group and 15 [4.6%] patients in the EU-Humira treatment group). All the patients started proper tuberculosis prophylaxis except for 2 patients (1 patient each in both treatment group) who early terminated the study.

During Study CT-P17 3.1 up to Week 24, an abnormal, clinically significant chest x-ray result was reported for 1 (0.3%) patient in the EU-Humira treatment group at Week 14. This patient experienced a TESAE of pulmonary TB and discontinued study drug administration.

Active TBs (including PTs of Pulmonary tuberculosis and tuberculosis) were reported in 2 (0.6%) patients in the EU-Humira treatment group. No active TB was reported in the CT-P17 treatment group. Both patients were diagnosed with active TB based on culture for *Mycobacterium tuberculosis* and further investigations including the clinical signs and symptoms, chest X-ray, and/or computed tomography (CT) scan in accordance with the general guideline on TB and the study protocol.

For the first patient, chest X-ray was performed twice after the positive IGRA conversion at Week 12. First chest X-ray revealed abnormal results, and pneumonia or TB was suspected. After then, the patient performed a chest X-ray again that showed abnormalities specifically related to the symptoms of TB. The results of these tests were obtained via query answers and the descriptions in serious adverse event (SAE) page of eCRF and were not recorded in unscheduled visit folders of eCRF.

For the other patient, chest X-ray and CT scan were performed after the positive IGRA conversion at Week 12. A chest X-ray revealed increased parenchymal pulmonary structures and widened left lung cavity. With the microbial culture, pulmonary TB was diagnosed and narrative for this patient is provided.

Treatment Period II

At the EOS visit, 2 (0.3%) patients (1 [0.7%] patients in the Humira maintenance group and 1 [0.7%] patient in the switched to CT-P17 group) had positive IGRA results. Only one (0.7 %) patient in the Humira maintenance group had new positive IGRA conversion at the EOS visit. One patient in the switched to CT-P17 group who reported positive at the EOS visit already had positive IGRA conversion at Week 12.

Overall Period

During the evaluation, the applicant was requested to explain the high number of IGRA conversion and latent TB cases emerged during study CT-P17 3.1. The results using the final study data up to Week 52 were

discussed in the applicant's response. All positive IGRA conversion results during the study were reported as TEAE of either latent or active TB. A total of 30 (4.6%) patients (12 [3.7%] and 18 [5.6%] patients in the CT-P17 and EU-Humira treatment groups, respectively) had positive IGRA conversion up to Week 52. Latent TBs (defined as a positive result of IGRA with negative examination of chest X-ray) were reported for 28 (4.3%) patients (12 [3.7%] and 16 [4.9%] patients in the CT-P17 and EU-Humira treatment groups, respectively) up to Week 52. Active TBs (including preferred terms of pulmonary tuberculosis and tuberculosis) were reported for 2 (0.6%) patients in the EU-Humira treatment group and none in the CT-P17 treatment group up to Week 52. Only 1 (0.7%) patient in the EU-Humira maintenance group was newly confirmed as positive IGRA conversion at the EOS visit, after the second randomisation at Week 26. Accordingly, this patient newly reported a latent TB at the EOS visit.

Laboratory findings

Laboratory parameters

Phase III Study CT-P17 3.1 in patients with RA

Overall Period

In study CT-P17 3.1, majority of laboratory parameters had no CTCAE grade or were CTCAE grade 1 (mild) or grade 2 (moderate) for each laboratory parameter.

The most frequently reported CTCAE grade 3 or higher laboratory parameter as worst value during the overall period was neutrophil count decreased; grade 3 neutrophil count decreased was reported for 32 (4.9%) patients (18 [5.6%], 14 [4.3%], 17 [5.6%], 5 [3.3%], and 9 [5.9%] patients in the CT-P17, Humira, CT-P17 maintenance, Humira maintenance, and switched to CT-P17 groups, respectively) and grade 4 neutrophil count decreased was reported for 22 (3.4%) patients (10 [3.1%], 12 [3.7%], 10 [3.3%], 7 [4.6%], and 4 [2.6%] patients in the CT-P17, Humira, CTP17 maintenance, Humira maintenance, and switched to CT-P17 groups, respectively).

The second most commonly reported CTCAE grade 3 or higher laboratory parameters was hypertriglyceridemia; grade 3 hypertriglyceridemia was reported for 11 (1.7%) patients (4 [1.2%], 7 [2.2%], 4 [1.3%], 3 [2.0%], and 4 [2.6%] patients in the CT-P17, Humira, CT-P17 maintenance, Humira maintenance, and switched to CT-P17 groups, respectively) and grade 4 hypertriglyceridemia was reported for 2 (0.3%) patients (2 [0.6%] in the CT-P17 treatment group, 2 [0.7%] in the CT-P17 maintenance group, and none in the Humira, Humira maintenance, and switched to CT-P17 groups).

Phase I studies in healthy subjects

According to the CT-P17 1.3 clinical study report, Grade 3 and Grade 4 CPK increased was reported for 1 and 3 subjects in the CT-P17 AI treatment group, respectively. All these CPK increases in 4 subjects occurred 14, 28, 42 and 56 days after administering single dose of CT-P17, respectively, and all were transient. Investigator's interpretation was that these laboratory results were not clinically meaningful and there was no notable trends related with study drug. This is endorsed.

Overall, no notable differences in mean and median values of laboratory parameters between the CT-P17 and Humira treatment groups were seen in the main biosimilarity study CT-P17 3.1 or in Studies CT-P17 1.1, 1.2 and 1.3 with supportive safety data.

AI usability study CT-P17 3.2 in patients with RA

The majority of laboratory parameters had no CTCAE grade or were CTCAE grade 1 or 2 for each laboratory parameter. The only reported CTCAE grade 3 laboratory parameter as the worst value during the study was CPK increased in 1 (1.6%) patient and one grade 4 hypertryglyceridemia was reported for 1 (1.6%) patient. No action was taken with study drug for those 2 patients.

Vital Sign Measurements, Physical Findings and Other Observations Related to Safety

The results of vital sign measurements, ECG, physical examination and local site pain assessment revealed no marked differences between treatment groups in studies CT-P17 1.1, 1.2, 1.3, 3.1 and 3.2.

Immunological events

Comparative immunogenicity evaluations were conducted in three single dose studies in healthy volunteers (Studies CT-P17 1.1, 1.2, 1.3) and in one multiple-dose study in RA patients (Study CT-P17 3.1).

The drug tolerance of the assay used was sufficient for detection of clinically relevant amounts of ADA. In HV studies at least 10 ng/mL of ADA was detected adequately. In RA patients (Study CT-P17 3.1) at least 50 ng/mL of ADA was detected adequately at all time points up to Week 24.

In study CT-P17 1.1 (the main comparative study in healthy volunteers), 99/102 (97.1%) and 99/104 (95.2%) subjects in the CT-P17 and EU-Humira treatment groups, respectively, showed a post-treatment ADA positive response (up to Day 71). Among the subjects who had post-treatment positive ADA results, 79.8% and 84.8% subjects showed NAb positive response in the CT-P17 and EU-Humira treatment groups, respectively. The rates of ADA conversion and NAb conversion were comparable for CT-P17 and EU-Humira in healthy subjects following a single dose. The ADA titre results also showed comparable distribution among the CT-P17 and EU-Humira treatment groups in study CT-P17 1.1.

The detected ADA frequencies and NAb proportions were similar across all HV studies.

- **ADA formation in RA patients**

Study CT-P17 3.1 was the confirmatory efficacy and safety study in RA patients; a multiple-dose, randomised trial with a duration of 52 weeks.

Immunogenicity data from Treatment period I (up to Week 24) are presented in Table 40. The proportion of patients with ADA positive results up to Week 24 was overall comparable, yet slightly lower in the CT-P17 treatment group (Table 40).

Table 40 Frequency of positive ADA/NAb in Study CT-P17 3.1 up to Week 24 (Study CT-P17 3.1, Safety Population)

Visit	CT-P17 (N=324)	EU-Humira® (N=324)
	n/N (%)	
Week 0 (Pre-dose)		
ADA	11/324 (3.4%)	6/324 (1.9%)

NAb	4/11 (36.4%)	1/6 (16.7%)
Week 2		
ADA	43/324 (13.3%)	86/324 (26.5%)
NAb	15/43 (34.9%)	21/86 (24.4%)
Week 4		
ADA	79/324 (24.4%)	108/324 (33.3%)
NAb	35/79 (44.3%)	40/108 (37.0%)
Week 8		
ADA	80/324 (24.7%)	98/324 (30.2%)
NAb	59/80 (73.8%)	67/98 (68.4%)
Week 12		
ADA	88/324 (27.2%)	116/324 (35.8%)
NAb	72/88 (81.8%)	97/116 (83.6%)
Week 16		
ADA	91/324 (28.1%)	121/324 (37.3%)
NAb	85/91 (93.4%)	104/121 (86.0%)
Week 20		
ADA	96/324 (29.6%)	112/324 (34.6%)
NAb	92/96 (95.8%)	105/112 (93.8%)
Week 24		
ADA	93/324 (28.7%)	116/324 (35.8%)
NAb	83/93 (89.2%)	103/116 (88.8%)
Post-treatment (up to Week 24)		
ADA	143/324 (44.1%)	185/324 (57.1%)
NAb	111/143 (77.6%)	141/185 (76.2%)

Note: The proportion of ADA positive patients was calculated using the number of patients in the safety population. The proportion of NAb positive patients was re-calculated using ADA positive patients as a denominator. n: number of patients with the event, N: number of patients in each treatment group.

The proportion of patients with ADA/Nab positive results was overall comparable between treatment groups in treatment period II up to Week 52.

The proportion of patients who had ADA seroconverted was lower in CT- P17 (135 of 310 [43.5%] and 183 of 317 [57.7%] patients in CT-P17 and EU-Humira treatment groups, respectively) for Treatment Period I. The proportion ADA and NAb seroconversion were generally maintained up to Week 52 in all treatment groups; 138 of 292 [47.3%], 88 of 150 [58.7%] and 93 of 149 [62.4%] patients for ADA and 115 of 138 [83.3%], 70 of 88 [79.5%] and 67 of 93 [72.0%] patients for NAb in the CT-P17 maintenance, Humira maintenance and Switched to CT-P17 groups, respectively.

In patients with negative ADA results before the first study drug administration, the rate of ADA conversion (to ADA+) tended to be slower in CT-P17 treatment group, whereas the rate of NAb conversion (to NAb+) was comparable for both treatment groups in treatment period I.

During the maintenance treatment, ADA conversion was less frequent than in Treatment Period I. Of the patients who had no ADA positive result before week 26, 28/300 (9.3%) patients had positive conversion in

ADA (17/171 [9.9%] for the CT-P17 maintenance group, 4/66 [6.1%] for the Humira maintenance group, and 7/63 [11.1%] for the switched to CT-P17 group) (Table 41).

Table 41 Summary of Positive Conversion in ADA or NAb

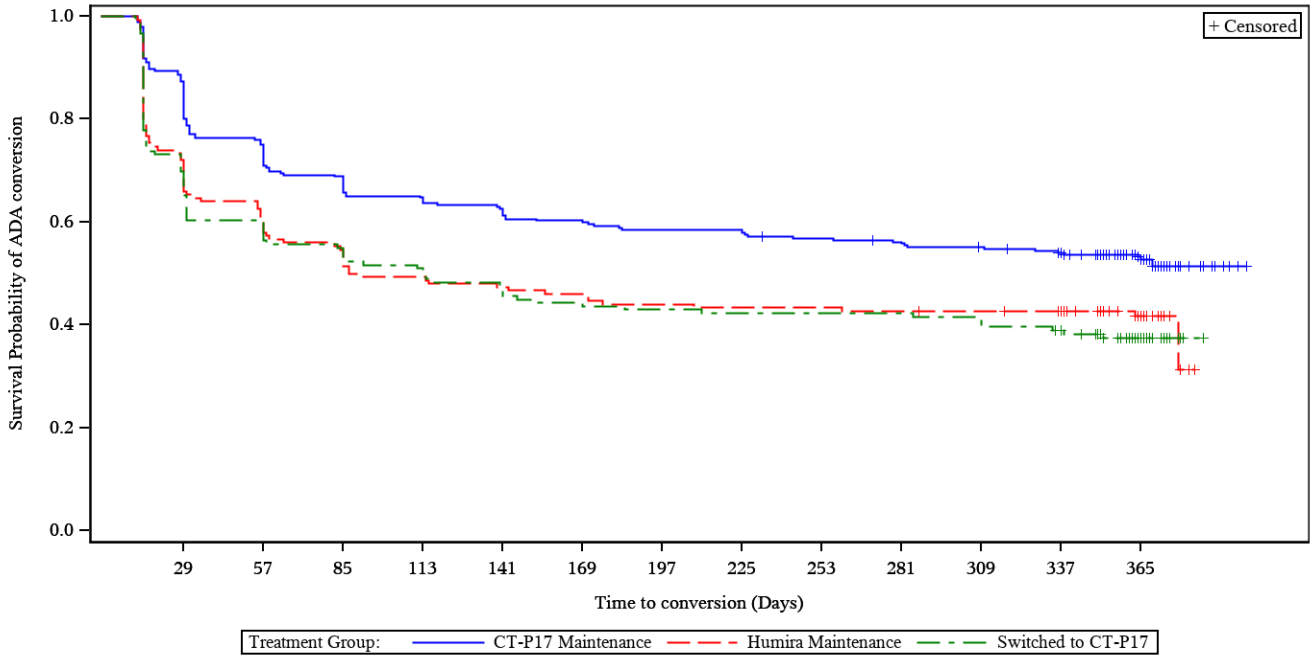
	CT-P17 (N=324)	Humira (N=324)	Total (N=648)
Treatment Period I			
Positive Conversion in ADA	135/310 (43.5%)	183/317 (57.7%)	318/627 (50.7%)
Positive Conversion in NAb	109/317 (34.4%)	144/322 (44.7%)	253/639 (39.6%)

	CT-P17 Maintenance (N=303)	Humira Maintenance (N=152)	Switched to CT-P17 (N=152)	Total (N=607)
Treatment Period II				
Positive Conversion in ADA	17/171 (9.9%)	4/66 (6.1%)	7/63 (11.1%)	28/300 (9.3%)
Positive Conversion in NAb	18/198 (9.1%)	3/83 (3.6%)	6/88 (6.8%)	27/369 (7.3%)

Abbreviations: ADA, antidrug antibody; NAb, neutralizing antibody.
Note: For Treatment Period I, the numerator is the number of patients with at least one ADA or NAb positive result after first study drug administration in Treatment Period I and before the first study drug administration in Treatment
Abbreviations: ADA, antidrug antibody; NAb, neutralizing antibody.
Note: For Treatment Period I, the numerator is the number of patients with at least one ADA or NAb positive result after first study drug administration in Treatment Period I and before the first study drug administration in Treatment

As shown in the Kaplan-Meier Plot of ADA/NAb conversion, switching from Humira to CT-P17 at week 26 did not have any significant effect on ADA conversion (Figure 8). The number (%) of patients who had positive ADA results at Week 52 was 86 (28.4%) patients in the CT-P17 maintenance group, 41 (27.0%) patients in the Humira maintenance group, and 43 (28.3%) patients in the switched to CT-P17 group.

Figure 8 Kaplan-Meier Plot of ADA Conversion



The ADA titre levels were comparable between the CT-P17 and EU-Humira treatment groups up to week 24 (Table 42). No data on titre levels by treatment group was provided for treatment period II.

Table 42 Subject Distribution by ADA Titre (Study CT-P17 3.1, ITT Population)

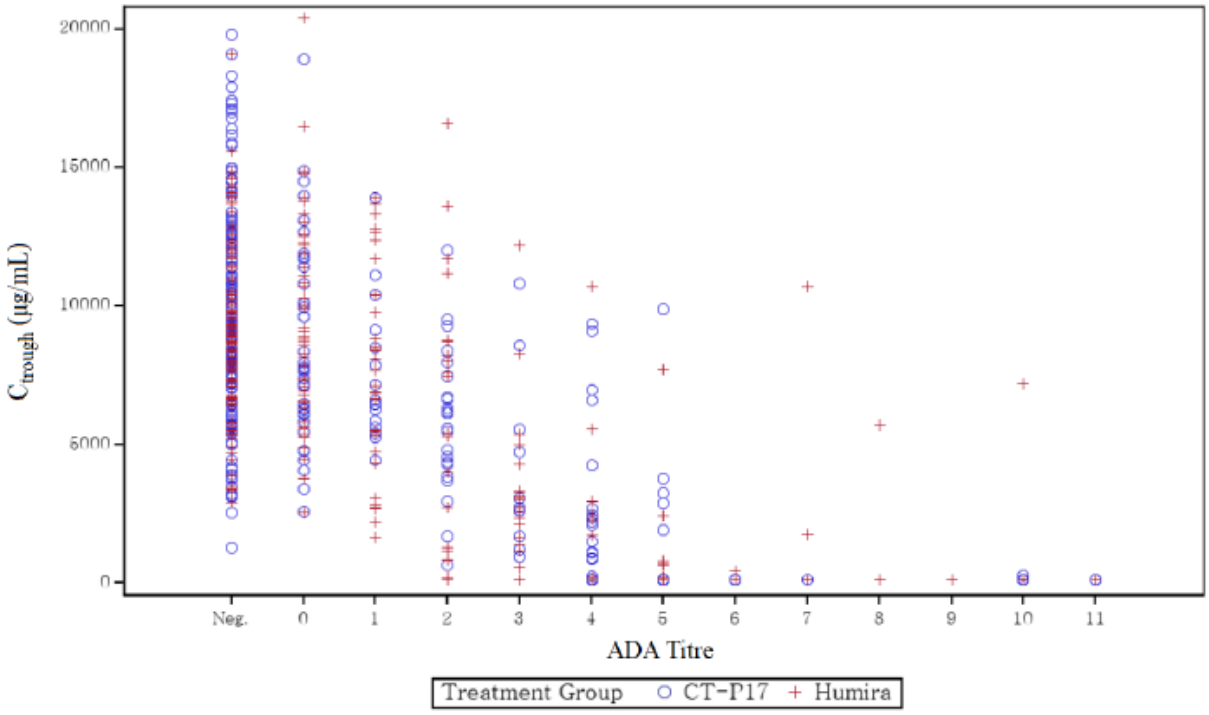
ADA Titer	CT-P17 (N=143)	Humira (N=185)
1	45 (31.5%)	53 (28.6%)
2	16 (11.2%)	33 (17.8%)
4	23 (16.1%)	21 (11.4%)
8	11 (7.7%)	21 (11.4%)
16	24 (16.8%)	19 (10.3%)
32	11 (7.7%)	9 (4.9%)
64	5 (3.5%)	9 (4.9%)
128	1 (0.7%)	4 (2.2%)
256	0	5 (2.7%)
512	0	5 (2.7%)
1024	5 (3.5%)	3 (1.6%)
2048	2 (1.4%)	3 (1.6%)

- **Impact of ADA on pharmacokinetics**

In Study CT-P17 3.1, subjects with ADA had lower adalimumab C_{trough} levels compared with those without ADA at any time point. The impact of ADA titre on C_{trough} was assessed up to "Week 22" (pre-dose of Week 24). A scatter plot of "Week 22" is presented in

Figure 9 9. The results show that the C_{trough} tends to be lower in the patients with higher titre. The trend was similar between the CT-P17 and EU-Humira treatment groups.

Figure 9 Scatter plot on ADA Titre vs C_{trough} at "Week 22" in Study CT-P17 3.1 (PK population)



Source: Section 5.3.5.3 Post-hoc Figure 5.08

Note: The maximum titre result of each patient after study drug exposure including unscheduled visit was used for analysis. Results of ADA titre was transformed using a log2-transformation.

In single-dose studies in healthy volunteers (study CT-P17 1.1; study CT-P17 1.2; study CT-P17 1.3), approximately 95% of subjects developed ADA. Subjects with ADA were divided into 3 titre groups (low, medium and high). As expected, within each treatment group the total exposure (AUC) decreased with increasing ADA titre, whereas C_{max} levels were not affected by ADA response. Importantly, comparable pharmacokinetics following a single dose was demonstrated between CT-P17 and Humira as well as between CT-P17 AI and CT-P17 PFS in all ADA titre groups.

The impact of ADA status on adverse events is presented in Table 43 and Table 44. During Study CT-P17 3.1, the proportion of patients who experienced any treatment-emergent adverse event (TEAE), treatment-emergent serious adverse event (TESAE), TEAE classified as hypersensitivity/allergic reactions and TEAE classified as injection site reactions were comparable between the CT-P17 and EU-Humira treatment groups in both ADA positive and negative subgroups. The frequency of treatment-emergent adverse events was slightly higher among ADA positive than among ADA negative patients. However, this slight difference is seen in similar magnitude in both treatment arms.

Table 43 Summary of Adverse Events by Post-treatment ADA Status in Study CT-P17 3.1 up to Week 24 (Safety Population)

Adverse events **ADA status**	**CT-P17** **(N=324)**	**EU-Humira®** **(N=324)**
Number (%) of patients with 1 ≥ TEAE		
Positive	83/143 (58.0)	113/185 (61.1)
Negative	86/178 (48.3)	71/138 (51.4)

Number (%) of patients with 1 ≥ TESAE		
Positive	6/143 (4.2)	8/185 (4.3)
Negative	4/178 (2.2)	8/138 (5.8)
Number (%) of patients with 1 ≥ TEAE classified as hypersensitivity/allergic reactions		
Positive	0	4/185 (2.2)
Negative	2/178 (1.1)	0
Number (%) of patients with 1 ≥ TEAE classified as injection site reactions		
Positive	8/143 (5.6)	14/185 (7.6)
Negative	8/178 (4.5)	8/138 (5.8)

Source: Section 5.3.5.3 Post-hoc Table 5.11. Note: Percentages are calculated by using the number of patients in each ADA subgroup as denominator.

There were no meaningful differences between treatment groups in the proportion of patients experiencing TEAEs for SOCs Infections and infestations, Investigations and General disorder and administrative site conditions *within the ADA-positive patient subgroups.*

Table 44 Summary of TEAEs by Post-treatment ADA Status in Study CT-P17 3.1 (Safety Population)

SOC ADA status	Treatment Period I*		Overall Period (2nd randomization group)		
	CT-P17 (N=324)	EU-Humira (N=324)	CT-P17 Maintenance (N=303)	EU-Humira Maintenance (N=152)	Switched to CT-P17 (N=152)
	Number (%) of Patients				
Infections and infestations					
Positive	56/145 (38.6)	73/188 (38.8)	70/148 (47.3)	45/89 (50.6)	43/96 (44.8)
Negative	45/176 (25.6)	39/135 (28.9)	55/155 (35.5)	29/63 (46.0)	25/56 (44.6)
General disorders and administrative site conditions					
Positive	11/145 (7.6)	21/188 (11.2)	10/148 (6.8)	8/89 (9.0)	10/96 (10.4)
Negative	15/176 (8.5)	10/135 (7.4)	15/155 (9.7)	6/63 (9.5)	5/56 (8.9)
Investigations					
Positive	18/145 (12.4)	14/188 (7.4)	21/148 (14.2)	5/89 (5.6)	19/96 (19.8)
Negative	16/176 (9.1)	14/135 (10.4)	22/155 (14.2)	8/63 (12.7)	8/56 (14.3)

* Total number of ADA positive subgroup up to Week 24 was 328 patients in the initial MAA. The total number increased to 333 when analysed up to Treatment Period I; 3 patients (one in CT-P17 treatment group, 2 in EU-Humira treatment group) with ADA conversion at Week 26 pre-dose and 2 patients (1 in CT-P17 treatment group and 1 in EU-Humira treatment group) who did not enter Treatment Period II but had ADA conversion after Week 26 were newly included in the ADA positive subset of Treatment Period I in this analysis.
Note: Percentages are calculated by using the number of patients in each ADA subgroup as denominator. For summary of Treatment Period I, ADA status obtained during Treatment Period I is applied. For summary of Overall Period, ADA status obtained during the entire study period is applied.

Discontinuation due to adverse events

Phase III Study CT-P17 3.1 in patients with RA

Treatment Period I

TEAEs leading to discontinuation of study drug were reported for 7 (2.2%) and 10 (3.1%) in the CT-P17 and EU-Humira treatment groups, respectively. All TEAEs leading to study drug discontinuation were reported for one patient in either treatment group except for hypersensitivity reported in 2 (0.6%) patients in the EU-Humira treatment group. The TEAEs leading to study drug discontinuation considered by the investigator to be related to the study drug were reported for 2 (0.6%) and 5 (1.5%) patients in the CT-P17 and EU-Humira treatment groups, respectively.

Treatment Period II

TEAEs leading to discontinuation of study drug were reported for 3 (1.0%), 2 (1.3%), and 5 (3.3%) patients in the CT-P17 maintenance, Humira maintenance, and switched to CT-P17 groups, respectively. All TEAEs leading to study drug discontinuation were reported for one patient in all treatment groups. The TEAEs leading to study drug discontinuation considered by the investigator to be related to the study drug were reported for 2 (0.7%), 1 (0.7%), and 2 (1.3%) patients in the CT-P17 maintenance, Humira maintenance, and switched to CT-P17 groups, respectively. One event of hepatitis B virus test positive was reported under the switched to CT-P17 group, but the event occurred before switching to CT-P17.

Overall Period

Overall, 27 (4.2%) patients experienced at least 1 TEAE leading to study drug discontinuation. The proportion of patients who experienced at least 1 TEAE leading to study drug discontinuation was similar between CT-P17 and Humira treatment groups (10 [3.1%] and 17 [5.2%], respectively), and among CT-P17 maintenance, Humira maintenance, and switched to CT-P17 groups (3 [1.0%], 3 [2.0%], and 5 [3.3%] patients, respectively).

Phase I studies in healthy subjects

In Study CT-P17 1.1, one subject in the CT-P17 treatment group discontinued study due to a TEAE reported as alopecia areata that occurred 27 days after administration of single dose of study drug. No subjects permanently discontinued from Studies CT-P17 1.2 and 1.3 due to TEAEs.

For comparison, according to the EPAR SmPC of Humira, the proportion of patients who discontinued treatment due to adverse events during the double-blind, controlled portion of pivotal studies was 5.9% for patients taking Humira and 5.4% for control treated patients.

AI usability study CT-P17 3.2 in patients with RA

One patient was discontinued from the study CT-P17 3.2 due to TEAE. This case considered the lower gastrointestinal haemorrhage that led to death, discussed above in section "Serious adverse events and deaths" of this AR.

2.5.1. Discussion on clinical safety

A total of 1,166 subjects were treated with CT-P17 or Humira in the clinical development programme for CT-P17. Safety findings are reported for 297 healthy subjects and 386 RA patients administered CT-P17 in the clinical development program. The size of the safety population is considered sufficient to the CHMP for evaluation of biosimilarity of safety.

The applicant's development programme included one pivotal Phase III confirmatory efficacy and safety study (CT-P17 3.1) in patients with RA. From the safety point of view, the objective of this study was to evaluate overall safety, including immunogenicity over 52 weeks. At the time of initial application's submission, the study was ongoing and data up to week 24 only were submitted. The missing long-term safety data up to 52 weeks were submitted upon CHMP's request during the procedure.

In addition to the pivotal biosimilarity study, safety data is also available from three Phase I single-dose studies in healthy subjects: Study CT-P17 1.1 (PK study for biosimilarity), Study CT-P17 1.2 (safety and PK pilot study), and CT-P17 1.3 (PK study between AI and PFS). The safety results from these studies are considered supportive.

The applicant's development programme also included an AI usability study (CT-P17 3.2) in 62 patients with RA. In this study, CT-P17 AI was administered 40 mg every other week for 24 weeks. At the time of initial application's submission, the study was still ongoing, and the applicant did not initially provide safety findings for Study CT-P17 3.2 except for the description of a death case occurred in this study. The safety data was submitted upon CHMP's request. Since the Study CT-P17 3.2 was not comparative, the information on overall safety of AI does not affect the overall assessment of biosimilarity but is considered supportive.

A pooled safety analysis was not performed, and safety results were reported per study.

During Treatment Period I up to 24 weeks of the study CT-P17 3.1, 989 TEAEs were reported in 367 (56.6%) patients, 175 (59.3%) patients in the CT-P17 treatment group and 192 (59.3%) patients in the EU-Humira treatment group. Proportion of patients reporting TEAEs considered by the investigator to be related to the study drug were comparable in CT-P17 (27.8%) and Humira (33.0%) treatment groups. In Treatment Period II until end-of-study visit at week 52, a total of 542 TEAEs were reported in 263 (43.3%) patients. The proportion of patients reporting at least one TEAE was quite similar among the three treatment groups: 39.9%, 45.4%, and 48.0% patients in the CT-P17 maintenance, Humira maintenance, and switched to CT-P17 groups, respectively. TEAEs considered by the investigator to be related to the study drug were reported in slightly more patients in the switched to CT-P17 group (23.7%) as compared to the CT-P17 maintenance (15.8%) and Humira maintenance (17.8.%) groups. During the Overall Period of study CT-P17 3.1, the proportion of patients reporting TEAEs as well as the proportion with TEAEs considered by the investigator to be related to the study drug were similar in patients that received either CT-P17 or Humira throughout the study.

During study CT-P17 3.1, TESAEs were reported slightly more often in Humira maintenance and switched to CT-P17 groups than in CT-P17 maintenance group. The proportion of patients with TESAEs considered by the investigator to be related to the study drug was similar among treatment groups.

Treatment-emergent adverse events leading to study drug discontinuation, including those considered by the investigator to be related to the study drug, were reported in similar extent in the treatment groups in study CT-P17 3.1.

As demyelinating disease, haematological reactions, heart failure, lupus-like syndrome and liver enzyme elevations are also known to be adverse events of special interest for adalimumab based on the SmPC of Humira SmPC and EPARs of some biosimilar adalimumab products. During the evaluation, the applicant was asked to provide data about their occurrence in clinical studies with CT-P17. The applicant responded that no events of demyelinating disease or lupus-like syndrome were reported in CT-P17 studies. Moreover, subjects with a history of moderate to severe heart failure were excluded from the CT-P17 studies.

Incidence of haematological reactions were similar for CT-P17 and EU-Humira in Study CT-P17 1.1 (3.9% and 2.9%, respectively), while somewhat higher incidence was observed in US-Humira group (5.9%). Incidences in study CT-P17 3.1 were similar for the two treatment arms within a certain period. In Period II, frequency of haematological reactions was the same in Maintenance CT-P17 group and the Switched to CT-P17 group. Interestingly, if PTs within Haematological reactions group are taken into account, the patient group switched to CT-P17 from EU-Humira at the 2nd randomisation (Week 26) experienced a higher incidence of the given haematological AE. This is the case for Neutropenia, Leukopenia and Thrombocytopenia PTs.

Leukopenia was observed in 7 (4.6%) patients of the switched to CT-P17 group, in 8 (2.6%) in the CT-P17 maintenance group and in none of the patients in Humira maintenance group during Treatment Period II. Of these 7 patients in the switched to CT-P17 group, 4 (2.6%) had experienced the same event in Treatment Period I. Leukopenia was reported in similar incidence in CT-P17 and Humira treatment groups during Treatment Period I (10 [3.1%] patients in the CT-P17 treatment groups. During the Overall Period, leukopenia was reported in 4.0% and 1.3% of patients in the CT-17 and Humira maintenance groups, respectively.

Definitely lower frequencies for haematological events as a whole as well as for the AEs within this group were found in study CT-P17 3.2 (study length: 28 weeks) even if they are compared with those obtained from study CT-P17 3.1 Treatment Period I (study period length: 26 weeks).

Frequencies of liver enzyme elevation-related AEs were slightly higher in CT-P17 arms of study CT-P17 1.1 and study CT-P17 3.1 through the Treatment Period II. However, in Treatment Period I of study CT-P17 3.1 a slightly higher incidence of liver enzyme elevations was found in EU-Humira arm. For patients, switched from EU-Humira to CT-P17 at Week 26, the same trend of increased frequency of liver enzyme elevation related AEs was observed as it was for some PTs from haematological reactions AE group. However, in the case of liver enzyme elevation AEs, this difference in AE frequencies between the two maintenance arms and the switched arm was much more pronounced than in case of haematological reactions-related AEs. For example, neutropenia AE was observed in 6.6% of patients in both maintenance groups of study 3.1/Period II, and in 9.2% of switched patients, and ALT increased AE was observed in 5.0%, 3.9% and 9.9% of patients in CT-P17 Maintenance, EU-Humira Maintenance and switched to CT-P17 arms of Study 3.1/Period II, respectively.

ALT increased was observed in 7 (4.6%) patients of the switched to CT-P17 group, in 8 (2.6%) in the CT-P17 maintenance group and in 1 (0.7%) patient in Humira maintenance group during Treatment Period II. Of these 7 patients in the switched to CT-P17 group, 2 (1.3%) had experienced the same event in Treatment Period I. ALT increased was reported in higher incidence in the Humira treatment group in Treatment Period I (3.4% of patients in the CT-P17 treatment group and 5.2% of patients in the Humira treatment group). During the Overall Period, proportion of patients reporting ALT increased were similar in patients that received same treatment throughout the study: 5.0% in the CT-P17 group and 3.9% in Humira group.

Liver enzyme elevations, as a whole occurred with frequencies of 7.3%, 5.9% and 13.2% in CT-P17 Maintenance, EU-Humira Maintenance and switched to CT-P17 arms, respectively. Same, but less pronounced trends could be found for AST and GGT elevations.

Overall, in studies CT-P17 1.1, 1.3 and also in Treatment Period I of study CT-P 3.1 and in case of maintenance arms of study CT-P17 3.1/Treatment Period II, there were no notable differences between CT-P17 and reference products in TEAEs of haematological reactions and liver enzyme elevations. For patients switched from EU-Humira to CT-P17 at Week 26 of study CT-P17 3.1, however, there were some trends of elevated AE frequencies in haematological reactions and liver enzyme elevations AE-groups. The applicant was requested by the CHMP to discuss this finding further. The applicant reviewed patients from CT-P17 switch subgroup having haematological or liver enzyme (LE)-related AEs on a case-by-case basis. These tabulated reviews included haematological or LE-related AEs in Treatment Period I of study CT-P173.1 as well as pre-study haematological or LE-related differences from normal laboratory values and other factors, which might predispose these patients for haematological and/or liver enzyme related AEs. For CT-P17 switch patients with haematological alterations, prior steroid use and/or pretreatment neutropenia, lymphopenia, leukopenia were revealed in most cases. Furthermore, in a majority of cases, the same haematological AE occurred for a given patient also in Treatment Period I. For CT-P17 switch patients with LE elevations, prior methotrexate use was revealed in all but one case. In addition, similar or same LE disorders were experienced for a given patient before the treatment initiation and/or in the Treatment Period I. LE elevations experienced by patients in CT-P17 switch subgroup in Treatment Period I generally remained stable or improved during Treatment Period II. Taking into account these findings, the applicant's opinion that these alterations in frequencies of haematological AEs and LE-elevations in CT-P17 switch subgroup are most likely chance findings and not clinically meaningful. This is agreed by the CHMP.

In Study CT-P17 1.1, incidence of most common (≥5%) AEs were generally similar or lower for CT-P17 than for EU-Humira or US-Humira with the exception of injection site reaction AE (CT-P17 - 19.6%, EU-Humira - 18.3% or US- approved Humira - 15.7%). TESAEs occurred with low and comparable frequencies in CT-P17 and EU-Humira treatment groups and none of them was considered to be related to the treatment.

In Study CT-P17 1.2, the overall AE incidence rate and incidence of related AEs as well as AE frequency in Infections and Infestations SOC are consistently higher for CT P17 than for EU-Humira. Of note, overall number of subjects in ITT population was 30 in Study CT-P17 1.2.

No deaths were reported during Studies CT-P17 1.1, 1.2, 1.3 and 3.1. There was one death case due to lower gastrointestinal haemorrhage reported in the AI usability study CT-P17 3.2. In this case, which was assessed as unrelated to the study treatment, long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) while not taking any gastroprotective agents and heavy smoking were the probable risk factors for such a severe GI bleeding.

The percentages of patients with AESIs were comparable between CT-P17 and Humira groups in studies 1.1, and 1.2.

No notable differences in laboratory parameters or marked differences in vital sign measurements, ECG, physical examination results or in local site pain assessment between treatment groups were seen in studies CT-P17 1.1, 1.2, 1.3, 3.1 and 3.2.

In Study CT-P17 1.1, all subjects had a negative IGRA result at screening. At the end-of-study visit, positive IGRA results were reported for 1 (1.0%) subject in the CT-P17 and EU-Humira treatment groups each, and 2 (2.0%) subjects in the US-Humira treatment group, which were comparable results across the 3 treatment groups. Abnormal CS chest x-ray results as well as subjects with active TB were not reported.

No subjects in Studies CT-P17 1.2 and 1.3 had a positive IGRA result and abnormal chest X-ray results.

During Study CT-P17 3.1 up to Week 52, positive IGRA results were reported for 12 (3.7%) patients in the CT-P17 treatment group and 18 (5.6%) patients in the EU-Humira treatment group who had negative IGRA results at baseline. Upon CHMP's request, the applicant explained the number of IGRA conversion and latent TB cases emerged during this study. The applicant presented IGRA conversation data from other available adalimumab Phase 3 biosimilar studies that are comparable with those from CT-P17 Study 3.1. The higher incidence of latent TB AE in Study CT-P17 3.1 might be attributed to the difference in the definition of latent TB AE in different adalimumab biosimilar studies, criteria for latent TB AE seem stricter for Study CT-P17 3.1. Furthermore, in Study CT-P17 3.1, most patients were enrolled in Eastern European countries, particularly Poland (231 [71.3%] patients each in both treatment groups) where the incidence of TB is higher than the average in the EU/EEA countries, and this also could have contributed to the IGRA conversion. CHMP agreed with the applicant's conclusion that the incidences of both IGRA conversion and latent TB in Study CT-P17 3.1 are consistent with those reported with other adalimumab biosimilars.

Abnormal, CS chest x-ray result was reported for 1 (0.3%) patient in the EU-Humira treatment group at Week 14. This patient experienced a TESAE of pulmonary TB and discontinued study drug administration.

Although direct comparison of safety data between the AI usability study CT-P17 3.2 and the other CT-P17 studies is not reliable due to difference study settings, it is noticed that the proportion of patients reporting TEAEs, TESAEs, AESIs and TEAEs leading to study drug discontinuation were comparable or lower in study CT-P17 3.2 as compared to the studies CT-P17 3.1 and CT-P17 1.3. Higher incidence of TEAEs of SOC upper respiratory tract infection in study CT-P17 3.2 as compared to studies CT-P17 3.1 and 1.3. The applicant's hypothesis that this could have been due the study being conducted during fall and winter season is reasonable to the CHMP. The proportion of patients reporting TEAEs in SOC musculoskeletal and connective tissue disorders in study CT-P17 3.2 was similar or lower than CT-P17 PFS or Humira PFS groups in studies CT-P17 3.1 and CT-P17 1.3. This observation supports the conclusion that the AI presentation of CT-P17 is as safe as the PFS presentations with regard to the musculoskeletal and connective tissue adverse events.

Overall, the number and pattern of adverse events in the single-dose studies CT-P17 1.1, 1.2 and 1.3 as well as those in the AI usability study CT-P17 3.2 appear supportive for the conclusions of the pivotal safety study CT-P17 3.1.

Immunogenicity was assessed in three single dose studies in healthy volunteers (Studies CT-P17 1.1, 1.2, 1.3) and in one multiple-dose study in RA patients (Study CT-P17 3.1). The sampling schedules were adequate.

In the three HV studies, the proportion of subjects who had post-treatment ADA positive and NAb positive results was similar between the treatment groups. In study CT-P17 1.1 (the main comparative study in healthy volunteers), 97.1% and 95.2% subjects in the CT-P17 and EU-Humira treatment groups, respectively, showed a post-treatment ADA positive response. Among the subjects who had post-treatment positive ADA results, 79.8% and 84.8% subjects showed NAb positive response in the CT-P17 and EU-Humira treatment groups, respectively. The ADA titre results also showed comparable distribution among the CT-P17 and EU-Humira treatment groups in study CT-P17 1.1. The detected ADA frequencies and NAb proportions were similar across all HV studies.

In RA patients, the proportion of patients who had post-treatment ADA positive results up to Week 24 was overall comparable yet slightly lower in the CT-P17 treatment group; 44.1 % and 57.1 % for the CT-P17 and EU-Humira treatment group, respectively. Among ADA positive patients in study CT-P17 3.1, the ADA titre levels up to week 24 and the proportion of patients who were NAb positive were similar between treatment

groups. At week 24, 89.2% and 88.8% of ADA positive subjects in the CT-P17 and EU-Humira treatment groups, respectively, showed NAb positive response. Overall, the proportion of patients who had ADA seroconverted was lower in CT-P17 (135 of 310 [43.5%] and 183 of 317 [57.7%] patients in CT-P17 and EU-Humira treatment groups, respectively) for Treatment Period I. The proportion ADA and NAb seroconversion were generally maintained up to Week 52 in all treatment groups; 138 of 292 [47.3%], 88 of 150 [58.7%] and 93 of 149 [62.4%] patients for ADA in the CT-P17 maintenance, Humira maintenance and Switched to CT-P17 groups, respectively.

Low ADA titres were observed in a few percent of adalimumab-naive RA patients at baseline. The applicant provided several possible explanations for the presence of ADA at Baseline. The pre-dose ADA positive rates reported in each study are considered comparable to various results previously reported in adalimumab biosimilar studies. Based on additional analyses and break down of the data, the overall impact of pre dose ADA positivity on PK, efficacy and safety is in line with that seen in patients who had positive ADA result after first study drug administration. Hence, the pre-dose ADA positivity does not impact the conclusion on biosimilarity between CT-P17 and Humira.

The reported ADA and NAb frequencies were similar to those seen in previous RA studies with adalimumab. Recent products approved by EMA, applying more sensitive immunogenicity testing methods than those used during original MA of Humira, have reported ADA incidences in RA studies at about 30-56% at week 24.

Overall, in the pivotal comparative study in RA patients, the CT-P17 treatment group showed slightly lower immunogenicity compared to the EU-approved Humira treatment group in Treatment Period I. The proportion of patients with positive ADA results became similar between the treatment groups towards the end of study. According to the EMA Guideline on similar biological medicinal products containing monoclonal antibodies, a lower immunogenicity for the biosimilar does not preclude biosimilarity. Switching from Humira to CT-P17 at week 26 did not have any significant effect on ADA conversion.

The frequency of treatment-emergent adverse events was slightly higher among ADA positive than among ADA negative patients up to week 52. This slight difference is seen in similar magnitude in both treatment arms and therefore, does not raise concerns regarding biosimilarity.

2.5.2. Conclusions on the clinical safety

The safety profiles of CT-P17 and Humira were found similar in short-term and long-term use, up to 52 weeks. The data also shows sufficient similarity between CT-P17 and EU-Humira in terms of ADA formation, ADA titre levels, NAb formation and the impact of ADA formation on clinical parameters up to week 52.

From the safety point of view, CT-P17 is therefore considered by the CHMP similar to Humira.

2.6. Risk Management Plan

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk - Serious infections	Routine risk minimisation measures: • SmPC sections 4.2, 4.3, 4.4, 4.5 and 4.8 • PL section 2 and 4 Legal status: Prescription only medicine Additional risk minimisation measures: Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Important identified risk - Tuberculosis (TB)	Routine risk minimisation measures: • SmPC sections 4.2, 4.3, 4.4 and 4.8. • PL sections 2 and 4 Legal status: Prescription only medicine Additional risk minimisation measures: Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Important identified risk - Malignancies	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 • PL sections 2 and 4 Legal status: Prescription only medicine Additional risk minimisation measures: Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk - Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis [ON])	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8. • PL sections 2 and 4 Legal status: Prescription only medicine Additional risk minimisation measures: Patient reminder card.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Important identified risk - BCG disease following live BCG vaccination in infants with in utero exposure to Yuflyma	Routine risk minimisation measures: • SmPC section 4.4 and 4.6 • PL section 2 Legal status: Prescription only medicine Additional risk minimisation measures: Patient reminder card.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Important potential risk - Progressive multifocal leukoencephalopathy (PML)	Routine risk minimisation measures: Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Important potential risk - Reversible posterior leukoencephalopathy syndrome (RPLS)	Routine risk minimisation measures: Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		Additional pharmacovigilance activities: None
Important potential risk - Adenocarcinoma of colon in ulcerative colitis (UC) patients	Routine risk minimisation measures: • SmPC section 4.4 Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Missing information - Patients with Immune Compromised conditions	Routine risk minimisation measures: • SmPC section 4.4. • PL section 2. Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Missing information - Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease (CD)	Routine risk minimisation measures: Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information - Episodic treatment in psoriasis (Ps), ulcerative colitis (UC), and juvenile idiopathic arthritis (JIA)	Routine risk minimisation measures: Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Missing information - Long-term safety information in the treatment of children with uveitis	Routine risk minimisation measures: • SmPC section 4.2 Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

The CHMP and PRAC considered that the risk management plan version 0.2 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the*

readability of the label and package leaflet of medicinal products for human use.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Yuflyma (adalimumab) is included in the additional monitoring list as it is a biological product.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Yuflyma was developed as a biosimilar to the reference medicinal product Humira. The route of administration (subcutaneous), posology, and indications are according to the reference product as described in the Humira SmPC.

The applicant applied for the same therapeutic indications as approved for Humira: rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (PJIA), active enthesitis-related arthritis, axial spondyloarthritis (ankylosing spondylitis [AS], and axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis (PsA), adult and paediatric plaque psoriasis (PsO), adult and paediatric Crohn's disease (CD), ulcerative colitis (UC), adult and adolescent hidradenitis suppurativa (HS), adult and paediatric non-infectious uveitis (UV).

The following strength and pharmaceutical forms are proposed: adalimumab 40 mg solution for injection in pre-filled syringe and in pre-filled pen.

Summary of quality comparability data

A comprehensive similarity exercise following the general principles outlined in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance; Quality issues (EMA/CHMP/BWP/247713/2012) has been performed. Several batches of CT-P17 and Humira-EU were included in the similarity study. The batches reflected a range of expiration dates and product ages. The similarity analyses were performed side-by-side using qualified in-house reference standard. The quality range was set by analysis of several batches of Humira-EU for key biological quality attributes. Qualified state of-the-art physicochemical and biological methods were used in the similarity assessment. Overall strategy included, when differences were observed, to evaluate the potential of these on safety, efficacy, PK/PD and immunogenicity.

Qualified state of-the-art physicochemical and biological methods were used in the similarity assessment. Analytical comparability studies included primary, secondary and higher order structures, post translational modifications (charge variants and glycan profiles), purity and impurities, quantity, biological activity of Fab and Fc related functions, and comparative stability studies.

Summary of non-clinical comparability data

A stepwise risk-based comparative approach has been followed to provide a totality of evidence for demonstrating biosimilarity. The nonclinical studies included *in vitro* primary pharmacodynamic studies (same

functional studies as in quality data) and one *in vivo* 28-day repeat-dose toxicity study (with toxicokinetics and immunogenicity testing) in cynomolgus monkeys to compare CT-P17 with Humira-EU.

Non-clinical studies were carried out with CT-P17 finished product manufactured from an early pilot scale finished product process, which was demonstrated comparable with CT-P17 used for analytical similarity and clinical studies.

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

Summary of clinical comparability data

Clinical efficacy, safety, immunogenicity and PK were assessed in three single dose studies studies in healthy volunteers (HV) and two multiple dose studies in RA patients (Studies CT-P17 1.1, 1.2 and 3.1 for biosimilarity; Studies CT-P17 1.3 and 3.2 for device development).

The pivotal PK study for biosimilarity (Study CT-P17 1.1) was a phase 1, randomised, double-blind, three-arm, parallel group, single-dose study in healthy 312 volunteers (CT-P17 PFS: 103, EU-Humira PFS: 106 and US-Humira PFS: 103). The subjects received a single PFS SC injection of study drug 40 mg/0.4 ml (100 mg/mL) and were followed up for 71 days.

The confirmative efficacy and safety study (CT-P17 3.1) was a randomised, double-blind equivalence study comparing CT-P17 and EU-Humira (40 mg SC every 2 weeks) in combination with MTX in subjects with moderately to severely active RA with inadequate response to MTX therapy (648 subjects randomised 1:1). The treatment duration was 52 weeks.

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

3.2. Results supporting biosimilarity

Quality data

Similarity between CT-P17 and Humira-EU has been demonstrated for the following physico-chemical and biological properties:

- Primary structure
- Higher order structure
- Content and extractable volume
- Size heterogeneity
- Charge variants
- Glycan profiles
- Binding to soluble and transmembrane TNFα
- Neutralisation of TNF α
- Reverse signalling activity
- Binding to Fc-receptors (FcγRIIIa [V, F], FcγRIIIb, FcγRIIa, FcγRIIb, FcγRI and FcRn)
- Binding to C1q and CDC activity

- ADCC activity
- Inhibition of TNFα-induced apoptosis
- Inhibition of IL-8 and VCAM-1 release
- Induction of regulatory macrophages and subsequent T-cell anti-proliferation.
- Stability under accelerated and stressed conditions and forced degradation

Nonclinical data

In vitro functional studies supporting biosimilarity mentioned under biological properties in quality results are the same.

Clinical data

Pharmacokinetics

Results for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and C_{max} in study CT-P17 1.1 demonstrate that the 90% CI for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% when comparing CT-P17 with the reference product from EU as well as from US.

In patients with moderate to severe active RA (study CT-P17 3.1), the mean C_{trough} of adalimumab was 9% to 13% higher in the CT-P17 treatment group over the first 24 weeks of study CT-P17 3.1. From the PK perspective, the difference in mean C_{trough} levels is not compelling evidence against biosimilarity between CT-P17 and Humira.

Efficacy

In patients with moderate to severe active RA (study CT-P17 3.1), 268/324 (82.72%) patients in the CT-P17 40mg SC EOW treatment arm and 268/324 (82.72%) patients in the EU-Humira 40mg SC EOW treatment arm (ITT population) achieved response according to ACR20 at week 24. The response rates are comparable to those seen in previous trials with Humira. The 95% CI for the estimate of treatment difference in ACR20 response rates at week 24 was entirely within the predefined equivalence margin of -15% to 15% for both ITT and PP populations. The results were unchanged after controlling for country and disease activity. Hence, the primary objective of this trial was met.

The treatment arms were highly similar in all secondary efficacy endpoints (ACR50, ACR70, hybrid ACR response, DAS28, EULAR response, CDAI, SDAI, quality of life [SF-36]). In particular, a high degree of similarity was also seen on the continuous DAS28(CRP) disease activity symptom rating scale, which adds to the robustness of the results.

Data from the second treatment period showed that efficacy was sustained up to week 52 in a comparable manner in all three treatment arms: CT-P17 and Humira maintenance groups as well as in patients who switched to CT-P17 at week 26.

The proportions of patients achieving response according to ACR20 at week 24 was only slightly lower among ADA positive than among ADA negative patients in the EU-Humira arm. The difference between ADA positive and ADA negative patients was smaller in the CT-P17 treatment arm. Among ADA positive subjects 83.2% and 80.0% in the CT-P17 and EU-Humira treatment group, respectively achieved response according to ACR20 at week 24 (ITT population). The corresponding response rates among ADA negative subjects were 83.7% and 87% in the CT-P17 and EU-Humira treatment group, respectively.

Throughout the whole 52 week study, when not impacted by an immune response, the efficacy of CT-P17 was similar to that of Humira in both short and long term treatment and also in patients who switched from Humira to CT-P17.

Safety

No major concerns regarding safety aspects of similarity have emerged based on assessment of data from the pivotal study CT-P17 3.1. In general, the number and pattern of TEAEs and proportion of patients reporting them were similar in CT-P17 group and EU-Humira group and are in line with expectations from historical data for Humira and its previously approved biosimilars. No major differences in frequency or pattern of TESAEs, TEAEs leading to discontinuation of study drug or AESIs were seen between treatment groups.

The safety results available from already completed Phase I single-dose studies in healthy subjects are considered supportive of the currently available pivotal safety data.

Immunogenicity

Data from HV studies 1.1 and 1.2 support similarity between CT-P17 and EU-Humira in terms of ADA formation, ADA titre levels and NAb proportions. Data from HV study 1.3 support similarity between AI and PFS presentations in the same parameters.

The data from RA patients (Study CT-P17 3.1) shows similarity between CT-P17 and EU-Humira in terms of ADA formation, ADA titre levels, NAb formation and the impact of ADA formation on clinical outcome (PK, efficacy and safety) up to week 52. The proportion of patients who had post-treatment ADA positive results up to Week 24 was 44.1 % and 57.1 % for the CT-P17 and EU-Humira treatment group, respectively. Switching from Humira to CT-P17 at week 26 did not have any significant effect on ADA conversion.

3.3. Uncertainties and limitations about biosimilarity

None

3.4. Discussion on biosimilarity

Quality

A comprehensive similarity exercise following the general principles outlined in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance; Quality issues (EMA/CHMP/BWP/247713/2012) has been performed. The comparability studies have been done by analysing several batches of CT-P17 and Humira-EU, side-by-side with qualified state of-the-art physicochemical and biological methods. Overall strategy included, when differences were observed, to evaluate the potential of these on safety, efficacy, PK/PD and immunogenicity.

Similarity has been demonstrated for the studied quality attributes. The observed differences were small and overall unlikely to have a clinical impact. Minor differences noted were mainly in charge variants, afucosylated species and mannosylation, and were without implications to Fab and Fc -related functions.

Charge variants profiles of CT-P17 and Humira-EU were by large similar with the same five major peaks detected. All variants were biologically active. CT-P17 had a slightly higher level of Basic group 2, but the proportions of Basic group 2 was low i.e. 1.3 - 1.7 % in CT-P17 and 0.9 - 1.1% in Humira-EU. Variants in Basic group 2 were classified as product-related impurities.

Basic group 2 was found enriched with a specific variant, that was reported to exclusively appear in CT-P17, but in small quantities (34% of the Basic group 2, i.e. approximately 0.5%). Upon request, the applicant provided further discussion on potential impact of the variant on functional properties and safety. According to the applicant, the specific form is considered as product-related impurity, which can be controlled by IEC-HPLC at in process as well as DS and DP levels. It was emphasised, that the form was a biosynthetic variant, which is mostly removed during the downstream purification process, it is not a degradation product, and therefore it can be effectively controlled. Data from long term, accelerated and stress stability studies did not reveal any sizeable increase in % area basic group 2, therefore accumulation of the form during storage is not expected. Furthermore, the low amount of the variant (≤ 2% basic group 2) is unlikely to have impact on the functional properties of the CT-P17 active substance. This conclusion can be agreed upon.

Differences were noted in mannosylated and afucosylated glycans. High mannose species were higher in Humira -EU (5.5 – 7.5 %) in comparison to CT-P17 (2.8- 4.7%) and afucosylated species were lower in Humira-EU (1.0 - 1.2 %) than in CT-P17 (3.0 - 4.7 %). Consequently, the total afucosylated glycans (mannosylated glycans + afucosylated glycans) were in range of 6.55 – 8.73 % in Humira-EU and 5.81 – 8.03 % in CT-P17. The differences observed in the glycans did not result in a detectable difference in Fc-related biological activity. Upon request, the applicant included a new DS specification to control total number of afucosylated glycans. In conclusion, some minor differences in glycation profiles between Humira EU and CT-P17 are unlikely to be clinically meaningful.

Qualified analytical methods were used for the biosimilarity analysis to assess the Fab and Fc -related biological functions. CT-P17 is similar to Humira-EU in Fab-related functions i.e. binding to soluble and transmembrane TNFα, TNFα neutralisation, and apoptosis induced by reverse signaling following binding to tmTNFα. Furthermore, CT-P17 and Humira-EU were similar in Fc-related functional activities.

The ADCC assay used for the comparative studies is a reporter gene based assay. Considering that this is not an endpoint assay, the relevance of the results is questionable. In order to demonstrate similar ADCC activity between CT-P17 and EU-Humira, the applicant provided a comparative ADCC activity results using PBMC from healthy donors. Although the genotype of PBMC was not clarified, this is acceptable considering the overall data, especially demonstrating that there were no differences in the FcγRIIIa binding activity and in previous ADCC reporter assay.

Non-clinical

The side-by-side *in vitro* nonclinical data are paramount for demonstration of biosimilarity from the nonclinical point of view. No such quality or non-clinical differences were found that would likely have an impact on the efficacy or safety of the CT-P17 in comparison to the Humira-EU. The applicant provided further information on methodologies, the concentration-effect curves, Kd, EC50 or IC50 values. This data verifed the data adequacy from which the conclusions of functional similarity was drawn. Overall, the functional *in vitro* data demonstrated, that CT-P17 and Humira-EU are similar.

The finding of adalimumab contamination in the formulation buffer in the toxicological (and TK) study in cynomolgus monkeys was confirmed, but the exact cause of the origin of the contamination was not identified. Consequently, this study cannot be considered fully valid. Nevertheless, considering the supplemental role of toxicological studies for biosimilars, this issue was not pursued by the CHMP as it would not have an impact for the overall conclusion on the similarity of CT-P17 and EU-Humira.

Clinical

Pharmacokinetics

Results for primary PK parameters $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ and C_{max} in study CT-P17 1.1 support the conclusion of biosimilarity of CT-P17 to the EU reference product.

Efficacy

The efficacy endpoints in the pivotal study 3.1 were validated and in line with what has been used in previous applications for products with RA indication. The efficacy was similar in both ITT and PP populations from week 0 to week 24 in terms of both primary and secondary efficacy outcomes. Data from the most sensitive time points (weeks 8-16) and from the more sensitive population of analysis (PP) confirmed similarity in efficacy according to ACR criteria between CT-P17 and Humira. Similar efficacy was maintained also after switching to CT-P17 at week 26 and up to week 52.

Safety

The safety data up to 52 weeks from the study CT-P17 3.1 indicated similar incidence and pattern of TEAEs, TESAEs, AESIs (hypersensitivity/allergic reactions, injection site reactions, infections and malignancies) between the CT-P17 and EU-Humira treatment groups. No new or unexpected safety findings were evident.

Safety data from the three Phase I single-dose studies are supporting of the pivotal data as no clear safety differences or issues were detected in these studies.

Immunogenicity

Similarity between CT-P17 and EU-Humira in terms of ADA formation, ADA titre levels, NAb formation and the impact of ADA formation on clinical parameters was shown. While ADA conversion was slightly less frequent with CT-P17 than with Humira, a lower immunogenicity for the biosimilar does not preclude biosimilarity according to the EMA Guideline on similar biological medicinal products containing monoclonal antibodies.

3.5. Extrapolation of safety and efficacy

All indications granted for the originator EU approved Humira are applied for Yuflyma. These include rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), active enthesitis-related arthritis, axial spondyloarthritis (ankylosing spondylitis [AS], and axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis (PsA), adult and paediatric plaque psoriasis (Ps), adult and paediatric Crohn's disease (CD), ulcerative colitis (UC), adult and adolescent hidradenitis suppurativa (HS), adult and paediatric non-infectious uveitis (UV).

As referenced by the applicant, the mechanism of action (MoA) of adalimumab therapy is primarily based on both inhibition of pro-inflammatory effects such as apoptosis, cell proliferation and cytokine secretion, and stimulation of anti-inflammatory effects through reverse signalling. Although the MoA of adalimumab is not completely elucidated, it is well accepted that adalimumab acts as a TNFα antagonist by binding to and neutralising soluble TNFα (sTNFα) and tmTNFα.

Neutralisation of sTNFα is a common mechanism across the non-IBD indications (RA, JIA, AS, PsA, Ps, HS, and UV), and the primary mechanism by which adalimumab particularly exerts its effect.

In addition to neutralisation of sTNFα, tmTNFα binding is considered to play a key role in treatment of the IBD indications (CD and UC).

Other mechanisms that could contribute to the biological activity of adalimumab include Fc-mediated binding which could induce ADCC, CDC and regulatory macrophage activation although the balance of evidence suggests that ADCC and CDC do not play a major role if any.

Based on a comprehensive comparability exercise where the similarity in potency and drug related effects on Fc-receptors and effector cells has been studied in non-clinical *in vitro* studies, CT-P17 was found to be highly similar to EU-Humira across all studied known and suggested modes of action, supporting extrapolation of efficacy to all indications.

Results for primary PK parameters $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and C_{max} support the conclusion of biosimilarity of CT-P17 to EU-Humira.

To conclude, extrapolation of the results to all indications approved for the originator is supported by the similarity shown in structural analysis, functional assays and the clinical similarity of PK, efficacy, safety and immunogenicity.

3.6. Additional considerations

Not applicable

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Yuflyma is considered biosimilar to Humira. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Yuflyma is favourable in the following indication:

Rheumatoid arthritis

Yuflyma in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Yuflyma can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Yuflyma in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Yuflyma can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1). Adalimumab has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Yuflyma is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1).

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Yuflyma is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Axial spondyloarthritis without radiographic evidence of AS

Yuflyma is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs).

Psoriatic arthritis

Yuflyma is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1) and to improve physical function.

Psoriasis

Yuflyma is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Paediatric plaque psoriasis

Yuflyma is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Hidradenitis suppurativa (HS)

Yuflyma is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy (see sections 5.1 and 5.2).

Crohn's disease

Yuflyma is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's disease

Yuflyma is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

Yuflyma is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Uveitis

Yuflyma is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

Paediatric uveitis

Yuflyma is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP

presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Yulfyma in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority. The educational program consists of a Patient Reminder Card.

The patient reminder card contains important safety information that a patient needs to be aware of before and during the treatment with Yuflyma. This reminder card is aimed at highlighting the risk of serious infections, tuberculosis (TB), malignancies, demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis [ON]) and BCG disease following live BCG vaccination in infants with in utero exposure to Yuflyma.

The MAH shall ensure that in each Member State where Yuflyma is marketed, all healthcare professionals who are expected to prescribe adalimumab and all patients who are expected to use adalimumab have access to/are provided with the following educational materials:

The Patient Reminder Cards (adult and paediatric) contain the following key elements

▪ That treatment with Yuflyma may increase the risk of infections, including tuberculosis, cancer and nervous system problems;
▪ Signs or symptoms of these safety concerns and when to seek attention from a healthcare professional;
▪ Importance of not receiving live vaccines and informing the health professional that the patient is receiving treatment in case of pregnancy;
▪ Instructions to record the brand name and batch number of the medication to ensure traceability;
▪ Contact details of the adalimumab prescriber.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.