12 December 2024
EMA/10943/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Avtozma

International non-proprietary name: tocilizumab

Procedure No. EMEA/H/C/006196/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

ACR	American College of Rheumatology
ACR20	American College of Rheumatology definition of a 20% improvement criterion
ACR50	American College of Rheumatology definition of a 50% improvement criterion
ACR70	American College of Rheumatology definition of a 70% improvement criterion
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
AET	Analytical evaluation threshold
AI	Auto-injector
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
anti-CCP	Anti-cyclic citrullinated peptide
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
ATCC	The American Type Culture Collection
AUC_t	Area under the concentration-time curve from 0 to the time of the last quantifiable observation
AUC_{inf}	Area under the concentration-time curve from 0 to infinite
AUC	Analytical ultracentrifugation
BLQ	Below the limit of quantification
BP	Blood pressure
CAPA	Corrective and preventive action
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
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence interval
CIPC	Critical in-process Control
CIPT	Critical in-process test
CLT1/2	Celltrion 1/2
C_{max}	Maximum serum concentration
COVID-19	Coronavirus disease-19
CPP	Critical process parameter
CQA	Critical quality attributes
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSR	Clinical study report
CT-P47	Corporate code of tocilizumab
CTD	Common technical document

CV	Coefficient of variation
DAS28	Disease activity score using 28 joint counts
DMARD	Disease-modifying antirheumatic drug
DNA	Deoxyribonucleic acid
DP	Drug product
DRM	Data review meeting
DS	Drug substance
DSC	Differential scanning calorimetry
DTNB	5, 5'-dithiobis-(2-nitrobenzoic acid)
ECG	Electrocardiogram
ECLA	Electrochemiluminescence assay
EDTA	Ethylenediaminetetraacetic acid
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
EM(E)A	European Medicines Agency
EOS	End of study
EPCB	End of production cell bank
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
Fab	Fragment antigen-binding
FBS	Foetal bovine serum
Fc	Fragment crystallisable
FcRn	Neonatal Fc receptor
FcγR	Fragment crystallisable gamma receptor
FDA	U.S. Food and Drug Administration
FTIR	Fourier transform infrared spectroscopy
GCA	Giant cell arteritis
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
HAQ	Health assessment questionnaire
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HC	Heavy chain
HCCF	Harvested cell culture fluid
HCP	Host cell protein
HCV	Hepatitis C virus
HILIC-UPLC	Hydrophilic interaction liquid chromatography - ultra performance liquid chromatography
HIV	Human immunodeficiency virus
HMW	High molecular weight
HPLC	High performance liquid chromatography
IB	Investigator's brochure
ICF	Informed consent form

ICH	International Council for Harmonisation
icIEF	Imaged capillary iso-electric focusing
IDMC	Independent Data Monitoring Committee
IEC	Ion exchange chromatography
IEC	Independent ethics committee
IGF-1	Insulin-like growth factor 1
IgG	Immunoglobulin G
IGRA	Interferon-γ release assay
IL-6	Interleukin-6
IL-6R	Interleukin 6 receptor
IM	Intramuscular
IPC	In-process control
IPT	In-process test
ISR	Incurred sample reanalysis
IV	Intravenous(ly)
IWRS	Interactive web response system
JAK-STAT	Janus kinase -signal transducer and activator of transcription
kDa	Kilodalton
kg	Kilogram
LAL	Limulus amoebocyte lysate
LC	Light chain
LC-ESI-MS	Liquid chromatography-electrospray ionisation-mass spectrometry
LC-MS	Liquid chromatography mass spectrometry
LER	Low endotoxin recovery
LIVCA	Limit of in vitro cell age
LLOQ	Lower limit of quantification
LRV	Log reduction value
LS	Least squares
mAb	Monoclonal antibody
Max	Maximum
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Multiple imputation
mIL-6R	Membrane-bound interleukin 6 receptor
Min	Minimum
mL	Millilitre
mM	Millimolar
MNAR	Missing not at random
MoA	Mechanism of action
MRD	Minimum required dilution
MTX	Methotrexate
MVM	Minute virus of mice
NAb	Neutralising antibody
NANA	N-acetylneuraminic acid
NGHC	Non-glycosylated heavy chain

NSAID	Non-steroidal anti-inflammatory drug
PAR	Proven acceptable range
PBMC	Peripheral blood mononuclear cell
PDE	Permitted daily exposure
PFS	Prefilled syringe
PFS-S	Pre-filled syringe with safety guard
Ph. Eur.	European Pharmacopoeia
PJIA	Polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetic
PPS	Per-protocol set
PRS	Primary reference standard
PRV	Pseudorabies virus
PS80	Polysorbate 80
PT	Preferred term
PTM	Post-translational modification
PV	Process validation
Q4W	Every 4 weeks
QA	Quality attribute
QC	Quality control
qPCR	Quantitative PCR
QR	Quality range
QTL	Quality tolerance limit
QTPP	Quality target product profile
RA	Rheumatoid arthritis
Reo-3	Reovirus type 3
RF	Rheumatoid factor
RH	Relative humidity
RMP	Reference medicinal product
RNA	Ribonucleic acid
RSD	Relative standard deviation
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDAI	Simplified disease activity index
SE	Standard error
SEC-HPLC	Size exclusion-high performance liquid chromatography
SEC-MALS	Size exclusion chromatography with multi-angle static light scattering
SF-36	36-item short form health survey
sIL-6R	Soluble interleukin 6 receptor
SJC28	Swollen joint count, number of swollen joints (0-28)
SJIA	Systemic juvenile idiopathic polyarthritis
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA Query
SOC	System organ class
SOP	Standard operating procedure
SPR	Surface plasmon resonance

SUSAR	Suspected unexpected serious adverse reaction
t_{max}	Time to maximum observed serum concentration
TEAE	Treatment-emergent adverse event
TEM	Transmission electron microscopy
TESAE	Treatment-emergent serious adverse event
TJC28	Tender joint count, number of tender joints (0-28)
TK	Toxicokinetic(s)
uDP	Unassembled drug product
UF/DF	Ultrafiltration/diafiltration
UK	United Kingdom
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
US	United States
USP	U.S. Pharmacopoeia
USPI	United states prescribing information
UV	Ultraviolet
VAS	Visual analogue scale
WCB	Working cell bank
WHO	World Health Organization
WRS	Working reference standard
X-MuLV	Xenotropic murine leukaemia virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celltrion Healthcare Hungary Kft. submitted on 9 February 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Avtozma, 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:

Avtozma 20 mg/mL concentrate for solution for infusion

Avtozma, in combination with methotrexate (MTX), is indicated for:

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma 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.

Avtozma is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Avtozma is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Avtozma can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Avtozma in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older.

Avtozma 162 mg solution for injection in pre-filled syringe

Avtozma, in combination with methotrexate (MTX), is indicated for

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma 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.

Avtozma is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Avtozma can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Avtozma in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients.

Avtozma 162 mg solution for injection in pre-filled pen

Avtozma, in combination with methotrexate (MTX), is indicated for

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma 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.

Avtozma is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 12 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids (see Section 4.2). Avtozma can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Avtozma in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 12 years of age and older, who have responded inadequately to previous therapy with MTX (see Section 4.2). Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: RoActemra, 20 mg/ml, Concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 16-01-2009
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/08/492/001, EU/1/08/492/002, EU/1/08/492/003, EU/1/08/492/004, EU/1/08/492/005, EU/1/08/492/006

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

- Product name, strength, pharmaceutical form: RoActemra, 20 mg/ml, Concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 16-01-2009
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/08/492/001, EU/1/08/492/002, EU/1/08/492/003, EU/1/08/492/004, EU/1/08/492/005 EU/1/08/492/006

And

- Product name, strength, pharmaceutical form: RoActemra, 162 mg, Solution for injection in pre-filled syringe
- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 23-04-2014
- Marketing authorisation granted by: Union
- Marketing authorisation number(s): EU/1/08/492/007, EU/1/08/492/008

And

- Product name, strength, pharmaceutical form: RoActemra, 162 mg, Solution for injection in pre-filled pen
- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 23-04-2014
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/08/492/009, EU/1/08/492/010

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: RoActemra, 20 mg/ml, Concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 16-01-2009
- Marketing authorisation granted by: Union
  - Marketing authorisation number(s): EU/1/08/492/001, EU/1/08/492/002, EU/1/08/492/005

And

- Product name, strength, pharmaceutical form: RoActemra, 162 mg, Solution for injection in pre-filled syringe
- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 23-04-2014
- Marketing authorisation granted by: Union

  - Marketing authorisation number(s): EU/1/08/492/007, EU/1/08/492/008
- Bioavailability study number(s): CT-P47 1.1, CT-P47 1.2, CT-P47 1.3

1.3. Information on paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

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

Date	Reference	SAWP co-ordinators
15 October 2020	EMEA/H/SA/4595/1/2020/III	Flora Musuamba Tshinanu and Dr Elena Wolff-Holz
25 March 2021	EMA/SA/0000050398	Linda Trauffler and Sheila Killalea
23 August 2021	EMA/SA/0000062435	Linda Trauffler and Sheila Killalea
24 February 2022	EMA/SA/0000072009	Andrea Laslop and Jens Reinhardt
23 June 2022	EMA/SA/0000087842	Anna Vikerfors and Sheila Killalea
14 July 2022	EMA/SA/0000098020	Anna Vikerfors and Sheila Killalea

The applicant received scientific advice on the development of a tocilizumab biosimilar (CT-P47) for treatment in the same indications as the reference product RoActemra from the CHMP on 15 October 2020 *(*EMEA/H/SA/4595/1/2020/III*)*. The scientific advice pertained to the following quality and clinical aspects:

- The sufficiency of the number of CT-P47 and reference product lots to be tested at each stage of development to confirm physicochemical and functional similarity; the suitability of the analytical and functional test methods to determine similarity of CT-P47 with reference product; the proposed stability testing program.
- The design of the comparative PK equivalence study in healthy volunteers (HV) using the intravenous formulation; the multi-tiered approach for immunogenicity testing for CT-P47 clinical study; the extrapolation to all currently authorised indications for RoActemra in the EU based on the PK equivalent study in HV.

The applicant received scientific advice on the development of a tocilizumab biosimilar (CT-P47) for

treatment in the same indications as the reference product RoActemra from the CHMP on 25 March 2021 (EMA/SA/0000050398). The scientific advice pertained to the following quality and clinical aspects:

- Changes in device components, risk assessment.
- Phase I comparative study design: inclusion exclusion criteria, dose, primary and secondary endpoints for PK parameters, sample size and equivalence margin, and study duration; Phase III comparative study design: route of administration, study population and inclusion exclusion criteria, dose, primary efficacy and secondary endpoints, sample size, power and equivalence margin; safety and immunogenicity profile.

The applicant received clarification on scientific advice EMA/SA/0000050398 from the CHMP on 23 August 2021 (EMA/SA/0000062435).

The applicant received scientific advice on the development of a tocilizumab biosimilar (CT-P47) for treatment in the same indications as the reference product RoActemra from the CHMP on 24/02/2022 (EMA/SA/0000072009). The scientific advice pertained to the following quality and clinical aspects:

- Source of active substance material for the Phase III study and for commercial supply.
- Risk assessment strategy for the intended administration devices vs those of the reference medicinal product and requirement for additional human factor validation or clinical usability studies

The applicant received scientific advice on the development of tocilizumab biosimilar (CT-P47) for treatment in the same indications as the reference product RoActemra from the CHMP on 23 June 2022 (EMA/SA/0000087842). The Scientific Advice pertained to the following quality and clinical aspects:

- Risk assessment of the administration devices, i.e. pre-filled syringe with safety guard (PFS-S) and auto-injector (AI); need for additional usability studies.

The applicant received clarification on scientific advice EMA/SA/0000087842 from the CHMP on 14 July 2022 (EMA/SA/0000098020).

1.6. Steps taken for the assessment of the product

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

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Beata Maria Jakline Ullrich

The application was received by the EMA on	9 February 2024
The procedure started on	29 February 2024
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	21 May 2024
The CHMP Co-Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	N/A
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	3 June 2024
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	27 June 2024

The applicant submitted the responses to the CHMP consolidated list of questions on	13 September 2024
The following GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the quality/safety/efficacy assessment of the product:	
– A GMP inspection to the site '' Binex Ltd, 3, Gaetbeol-ro, Yeonsu-gu, Incheon, 21999, Republic of Korea'' has been performed on 4-6 September 2024. The outcome of the inspection carried out was issued on 19/11/2024.	11 November 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of questions to all CHMP and PRAC members on	21 October 2024
The PRAC agreed on the PRAC assessment overview and advice to CHMP during the meeting on	31 October 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	14 November 2024
The applicant submitted the responses to the CHMP list of outstanding issues on	19 November 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	7 December 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Avtozma on	12 December 2024

2. Scientific discussion

2.1. Problem statement

Not applicable for a biosimilar.

2.2. About the product

CT-P47 (Avtozma) is a recombinant humanised monoclonal antibody that is being developed as a similar biological medicinal product to the reference medicinal product, EU-approved RoActemra.

Similar to the reference product, EU-approved RoActemra, CT-P47 has been developed for subcutaneous and intravenous administration. The applicant applies for the following dosage forms for this initial marketing authorisation application of CT-P47:

- 80 mg/4 mL (20 mg/mL) solution in a single-dose vial for intravenous infusion
- 200 mg/10 mL (20 mg/mL) solution in a single-dose vial for intravenous infusion
- 400 mg/20 mL (20 mg/mL) solution in a single-dose vial for intravenous infusion
- 162 mg/0.9 mL (180 mg/mL) solution in a single-dose pre-filled syringe with safety guard (PFS-S) for subcutaneous injection
- 162 mg/0.9 mL (180 mg/mL) solution in a single-dose prefilled pen (autoinjector [AI]) for subcutaneous injection

Tocilizumab recognises the IL-6 binding site of the human IL-6R and inhibits IL-6 signalling through competitive blockade of the IL-6 binding site. Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), thus inhibiting both classic signalling and trans-signalling in cells that express mIL-6R or gp130, respectively.

The proposed therapeutic indications conform to those of the originator product Roactemra:

Avtozma, in combination with methotrexate (MTX), is indicated for:

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma 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.

Avtozma is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. *(Only the concentrate for solution for infusion)*

Avtozma is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older (*concentrate for solution for infusion*)/ 1 years of age and older (*solution for injection in prefilled syringe*)/ 12 years of age and older (*solution for injection in pre-filled pen*) who

have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Avtozma can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Avtozma in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older (*concentrate for solution for infusion* and *solution for injection in prefilled syringe)/* 12 years of age and older *(solution for injection in pre-filled pen)*, who have responded inadequately to previous therapy with MTX. Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older. *(Only the concentrate for solution for infusion)*

Avtozma is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients. *(Only the solution for injection in prefilled syringe and in prefilled pen)*

2.3. Type of application and aspects on development

The applicant has received EMA scientific advice on chemical, pharmaceutical and biological development regarding biosimilarity, source of active substance material for the Phase 3 study and commercial supply, changes in device components during clinical studies, risk assessment strategy for the intended administration devices vs. those of the reference medicinal product and requirement for additional usability studies. The applicant has mostly followed the provided advice.

Originally, the applicant planned to only conduct one clinical study: a randomised, double-blind, three-arm, parallel-group, single dose, Phase I study to compare the PK similarity and safety of three intravenous infusion formulations of tocilizumab (CT-P47, RoActemra, and Actemra) in healthy male and female subjects. The clinical plan was modified based on CHMP SA to include altogether five clinical studies: three PK studies addressing both the SC and IV administration route and comparability of PK of tocilizumab administered with the prefilled syringe vs. the autoinjector; one Phase 3, randomised, active-controlled, double-blind, two-arm, parallel group, multiple-dose study to compare efficacy and safety of CT-P47 and EU-RoActemra (IV) co-administered with MTX in patients with moderate to severe active RA; and a usability study on the autoinjector. The clinical development is mostly adherent to the scientific advice given by the CHMP and the involved parties mostly reached consensus on the clinical development program. However, opinions differed on some issues like measuring PD markers in the Phase III trial.

2.4. Quality aspects

2.4.1. Introduction

Avtozma finished product (FP) is presented as:

- concentrate for solution for infusion containing 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL of tocilizumab as active substance (for intravenous use (IV)) in vials. Each mL of the concentrate contains 20 mg tocilizumab (20 mg/mL); and

- solution for injection containing 162 mg / 0.9 mL tocilizumab as active substance (for subcutaneous use (SC)) in pre-filled syringe (PFS) and pre-filled pen (PFP). Each PFS/PFP contains 162 mg of tocilizumab in 0.9 mL.

Other ingredients are: L-histidine, L-threonine, L-methionine, polysorbate 80 and water for injections.

The product is available in:

- a vial (type I glass) with a stopper containing 4 mL, 10 mL or 20 mL concentrate for solution for infusion. Pack sizes of 1 and 4 vials.
- a PFS (type I glass) with a staked-in needle, closed by a needle shield and a plunger stopper. The pre-filled syringe is available in packs containing: 1 pre-filled syringe, 4 pre-filled syringes, and 12 (3 packs of 4) pre-filled syringes (Multipacks).

a PFS (type I glass) with a staked-in needle assembled into a PFP. The syringe is closed by a needle shield and a plunger stopper. The pre-filled pen is available in packs containing: 1 pre-filled pen, 4 pre-filled pens and 12 (3 packs of 4) pre-filled pens (Multipacks)

2.4.2. Active substance

2.4.2.1. General information

Avtozma (tocilizumab, CT-P47) has been developed as biosimilar medicinal product to the reference medicinal product, EU-approved RoActemra. CT-P47 and EU-RoActemra are identical with respect to primary structure, components, concentration and route of administration (SC, IV).

CT-P47 is a recombinant humanised immunoglobulin (Ig) G1 monoclonal antibody (mAb) that specifically binds to both soluble and membrane-bound interleukin-6 receptors (IL-6R) blocking the activity of pro-inflammatory cytokines.

The proposed mechanism of action for CT-P47 is inhibition of IL-6-mediated signalling through specific binding to both soluble and membrane-bound IL-6 receptors.

Appropriate description of general information on CT-P47 has been provided.

2.4.2.2. Manufacture, characterisation and process controls

Manufacturers

The sites responsible for manufacture, testing and release of CT-P47 active substance (AS) have been provided. CT-P47 active substance is manufactured at Binex Ltd, 3 Gaetbeol-Ro 9, Yeonsu-gu, Incheon, Republic of Korea. Valid GMP Certification has been provided for Binex Co. Ltd following a Major Objection raised during the procedure. Valid proof of GMP compliance has been provided for all the sites involved in the manufacture of the active substance.

Description of manufacturing process and process controls

CT-P47 AS for commercial supply is manufactured using a Chinese hamster ovary (CHO) cell line. The CT-P47 AS manufacturing process is divided to upstream and downstream manufacturing steps. In addition to a narrative description of the manufacturing process, appropriate process flow charts with operational parameters, hold times and in-process tests are presented.

The upstream manufacturing process includes the following unit operations: seed expansion from WCB through a series of expansion steps, production, and harvest.

The downstream manufacturing process includes a series of chromatography steps, viral inactivation, and filtration, ultra/diafiltration (UF/DF), final filtration and filling.

The description of the AS manufacturing process is considered sufficiently detailed. Batch numbering system is adequately described in the dossier.

Control of materials

Raw materials used for the manufacture of CT-P47 are adequately presented. For compendial materials, reference is made to the Ph. Eur. or USP. For non-compendial raw materials, in-house acceptance criteria have been described.

History of cell line and generation of expression vector (coding heavy and light chain) is sufficiently described. Origin and function of expression vector components are adequately defined, and sequences of heavy and light chains are provided.

Appropriate description of the cell substrate generation including transfection, selection, screening and stability testing of the selected clones are presented in the dossier.

A traditional two-tiered cell banking system has been established. Master cell bank (MCB) and WCB have been manufactured from Pre-MCB and MCB, respectively. MCB was characterised extensively. Non-compendial test methods for cell bank characterisation and testing have been suitably qualified.

Specification for MCB and WCB re-qualification together with acceptance criteria are provided and are considered acceptable. The proposed tests and acceptance criteria for qualification of new WCB are considered appropriate. End of Product Cell Bank (EPCB) and cells at the limit of in vitro cell age (LIVCA) were adequately characterised.

Overall, the generation, characterisation and testing of cell banks are in line with ICH Q5B and ICH Q5D guidelines and are considered acceptable.

Control of critical steps and intermediates

The development of the control strategy and, overall, the approach to define criticality of process parameters and in-process tests have been described in line with relevant EMA guidelines.

The control strategy was developed by establishing quality target product profile (QTPP) and critical quality attributes (CQA). Descriptions of the analytical methods used for critical in-process tests and their validation/qualification status have been adequately provided.

Process validation

Process validation (PV) for CT-P47 AS was carried out at commercial scale at Binex, Incheon, Republic of Korea, which is the intended commercial manufacturing site for CT-P47.

Process validation was performed, and data are provided for each step. The results of PV runs met the pre-determined acceptance criteria. Based on the process validation data, it can be concluded that the process consistency has been demonstrated by the input and output parameters and controls repeatedly meeting their requirements.

Sufficient clearance of process related impurities was demonstrated. The presented data demonstrate that the CT-P47 AS manufacturing process clears process-related impurities to acceptable levels.

The process validation data provided is adequate and sufficient.

Manufacturing process development

Some changes and some process improvements were introduced during manufacturing process development. Justifications for the changes implemented to the manufacturing process are acceptable. Comparability of the different process versions has been addressed.

In conclusion and based on the data provided, CT-P47 AS manufactured according to the different process versions can be considered comparable. The differences were sufficiently assessed and justified and are not expected to impact clinical performance of the product.

Characterisation

Elucidation of structure and other characteristics

Extensive product characterisation has been performed using three CT-P47 AS batches manufactured using the commercial manufacturing process and some CT-P47 FP bathes derived from AS batches involved in the characterisation study. All tests were performed in a side-by-side manner to allow direct comparison of the data from CT-P47 AS and FP.

Characterisation was performed using state-of-the-art techniques and included determination of all relevant quality attributes. Overall, the performed characterisation studies are considered adequate. In addition, based on the comparable AS and FP characterisation results, the FP manufacturing process does not compromise the physicochemical quality or biological activities of the final product.

Impurities

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

Evaluation concerning nitrosamines has been provided. Applicant´s conclusions on the potential risk of nitrosamines being negligible, is agreed.

2.4.2.3. Specification

Specifications and justification of specification

The proposed specification for CT-P47 AS release includes compendial tests and non-compendial tests. The proposed panel of release tests cover identity, quantity, purity/impurity, potency, general tests, charge heterogeneity, glycosylation and safety.

In general, the panel of tests are in line with ICH Q6B and are considered appropriate for routine control of a monoclonal antibody at release. The proposed acceptance criteria for AS release and stability are adequately justified and acceptable. Aspects on historical data, analytical and manufacturing variability, regulatory guidelines, pharmacopoeial limits and published literature have been taken into account, when establishing the specification limits. The proposed end-of-shelf-life specification is identical to the proposed commercial specification for release except for the omission of some tests for attributes that are not expected to change over time.

Analytical procedures, validation of analytical procedures

Analytical methods have been adequately described. Compendial analytical methods are performed in accordance with the relevant Ph. Eur. monographs. The non-compendial method descriptions are sufficiently detailed and include details regarding equipment, reagents, operating conditions, sample and standard preparation, assay controls and system of suitability.

The analytical procedures have been appropriately validated in accordance with ICH Q2(R1). Verification data has been presented for all the compendial methods and the data presented shows

that all the verification results met the acceptance criteria, and the methods are considered appropriate for their intended use.

Batch analysis

Batch analyses data have been presented for several AS batches. Batch information include batch scale, manufacturing date and site, and batch usage. All batches were released as per the specification in place at the time of release. All results comply with the proposed commercial specifications.

Reference standards

The history of the in-house CT-P47 reference standards used throughout the development is adequately described. A two-tiered reference standard system with primary reference standard (PRS) and working reference standard (WRS) has been established for commercial manufacturing.

The current PRS was derived from CT-P47 AS batch representative of material used in clinical studies. The current WRS was derived from AS batch used in process validation and characterisation studies.

Qualification data demonstrated suitability of the PRS and WRS. Approach for introduction of future reference standards is presented.

The information provided is sufficient and acceptable.

Container closure

The container closures for CT-P47 AS are pre-sterilised bottles. Technical diagrams of the biotainers and representative certificates of analysis from the supplier are included in the dossier. Appropriate specifications for containers are in place.

Container closure integrity test was performed to study suitability of the containers for use. Results confirmed container integrity and product protection. According to the photostability studies, the AS is photo-sensitive and should be protected from light during storage. Compatibility of the container closure system with CT-P47 AS has been studied. The applicant has performed leachables/extractable studies. The information provided in this section is sufficient and acceptable.

2.4.2.4. Stability

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

The shelf-life for the CT-P47 AS stored at long-term condition was proposed based on the long-term, intermediated, accelerated and stressed stability data.

All currently available long-term stability results met the stability acceptance criteria and are within the limits defined for commercial specification. No significant trends are observed in the tested quality attributes. Based on the review of the stability data provided the proposed shelf-life is considered acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Description and composition of the finished product

The finished product is presented as:

- concentrate for solution for infusion containing 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL of tocilizumab as active substance (for intravenous use) in vials. Each mL of the concentrate contains 20 mg tocilizumab (20 mg/mL); and
- solution for injection containing 162 mg / 0.9 mL tocilizumab as active substance (for subcutaneous use) in pre-filled syringe (PFS) and pre-filled pen (PFP). Each PFS/PFP contains 162 mg of tocilizumab in 0.9 mL.

Other ingredients are: L-histidine, L-threonine, L-methionine, polysorbate 80 and water for injections.

The product is available in:

- a vial (type I glass) with a rubber stopper containing 4 mL, 10 mL or 20 mL concentrate for solution for infusion. Pack sizes of 1 and 4 vials.
- a PFS (type I glass) with a staked-in needle, closed by a rigid needle shield and a sterile elastomeric plunger stopper (with silicone). The pre-filled syringe is available in packs containing: 1 pre-filled syringe, 4 pre-filled syringes, and 12 (3 packs of 4) pre-filled syringes (multipacks).
- a PFS (type I glass) with a staked-in needle assembled into a PFP. The syringe is closed by a rigid needle shield and a sterile elastomeric plunger stopper (with silicone). The pre-filled pen is available in packs containing: 1 pre-filled pen, 4 pre-filled pens and 12 (3 packs of 4) pre-filled pens (multipacks).

CT-P47 FP (IV) is a sterile liquid solution containing 400 mg, 200 mg or 80 mg of CT-P47 active substance. Each vial is designed to deliver a single dose of 400 mg, 200 mg or 80 mg active ingredient in 20 mL, 10 mL or 4 mL, respectively, of solution at a nominal concentration of 20.0 mg/mL.

CT-P47 (SC) 162 mg FP is formulated for subcutaneous administration as a sterile, preservative free liquid solution in a pre-filled syringe intended to deliver 162 mg of CT-P47 active substance. Each syringe is designed to deliver a single dose of 162 mg CT-P47 active substance in a 0.9 mL of solution at a nominal concentration of 180 mg/mL.

Two devices will be registered with the CT-P47 FP:

- A pre-filled syringe with a safety guard (PFS-S) in which, in addition to the finger flange, the plunger rod, and the safety guard is assembled onto the CT-P47 unassembled drug product (uDP);
- An auto-injector (AI), a single-use, disposable device intended to deliver a fixed dose of FP, which consists of CT-P47 FP assembled with sub-assemblies.

The description and composition of both IV and SC FP is adequately described. The excipients in the formulation of CT-P47 IV are identical to those of CT-P47 SC. The only difference between CT-P47 SC and IV FP formulations are the protein concentrations and the PS80 concentrations. All excipients used in CT-P47 IV FP comply with Ph. Eur. requirements, are commonly used in the manufacturing of parenteral pharmaceutical preparations and are considered acceptable.

Formulation development

The formulation studies were designed to investigate and optimise a liquid formulation candidate that would stabilise tocilizumab. Full formulation development studies were conducted for CT-P47 FP and the final formulation was subsequently characterised.

Overall, the formulation development of CT-P47 has been adequately described and the results of the studies are appropriately presented and summarised in the dossier.

Overages

No formula overages are applied for CT-P47 SC or IV FP. To ensure the labelled dose of each strength can be withdrawn from 80 mg, 200 mg and 400 mg vial, volume overfill is applied.

Manufacturing process development

The CT-P47 400mg, 200mg and 80mg FP manufacturing process consists of preparation of formulation buffer, formulation of final bulk, filtration, aseptic filling, capping, and visual inspection.

The changes implemented for all IV FPs for different manufacturing processes have been clearly described and justified in the dossier.

Comparability has been studied in accordance with ICH Q5E between the different FP manufacturing processes and material from the different IV FP manufacturing processes can be considered comparable.

The CT-P47 SC FP manufacturing process consists of formulation of final bulk, sterile filtrations, aseptic filling and stoppering, and visual inspection processes. The changes implemented for CT-P47 SC FP manufacturing during product development have been clearly described and justified in the dossier.

Comparability has been studied in accordance with ICH Q5E between the different SC FP manufacturing processes and FP manufactured for SC and IV can be considered comparable.

Overall, the manufacturing process development for both CT-P47 IV and SC FP has been described in sufficient detail.

Container closure system

The container closure system for CT-P47 IV FP is composed of a 20 mL or a 4 mL type I glass vial, a rubber stopper and a flip-off cap. Comprehensive information on the container closure is presented and discussed. The stopper and vial comply with USP and Ph. Eur. requirements. The available leachable study data, shows no toxicological risk in CT-P47 finished product. It can be concluded that CT-P47 IV FP is compatible with the primary container closure system.

The primary container closure system for CT-P47 SC FP is composed of Type I glass pre-syringe with a plunger rod with sterile elastomeric plunger stopper with a staked-in needle. All components of primary container closure systems comply with USP and Ph. Eur. requirements. The primary container components in contact with the product are identical for the PFS-S and AI device configurations. The PFS-S and AI presentation only differ in having secondary device constituent parts (i.e. plunger rod, finger flange, and safety guard for the PFS-S and a Syringe unit and a Drive unit for the AI), which do not come into contact with the FP at any time. Based on the available data for the leachable study it can be concluded that there is no toxicological risk in CT-P47 SC FP.

Microbiological attributes of CT-P47 FP

The microbiological attributes of CT-P47 (IV and SC) FPs are controlled throughout the AS and FP manufacturing processes via bioburden and endotoxin testing. In addition, the FPs are sterile filtered and filled under aseptic conditions. The aseptic processes have been validated using media fill studies. All excipients are controlled by their respective pharmacopoeial monographs. Container closure integrity testing is performed to ensure the suitability of the container closure systems to prevent microbial contamination.

Compatibility

The compatibility of the CT-P47 IV FP with various types of infusion containers has been adequately studied. Based on the available data, it is concluded that CT-P47 IV finished product is compatible with the primary container closure system.

Compatibility with reconstitution diluents/equipment has not been studied for CT-P47 SC FP as the CT-P47 SC FP is a solution for injection in a pre-filled syringe intended for a single use. Stability studies do not indicate incompatibility issues between the active substance and excipients.

2.4.3.2. Manufacture of the product and process controls

A list of manufacturers responsible for the manufacture, quality control testing and release of CT-P47 IV FP has been provided.

For all the manufacturing sites involved in the manufacture, packaging, testing and QP release of CT-P47 FPs a valid proof of EU-GMP compliance has been provided.

Clear step-by-step descriptions of the CT-P47 IV and CT-P47 SC FP manufacturing processes with process flow charts for each manufacturing step have been provided for all manufacturing sites. The CT-P47 IV FP manufacturing process includes preparation of formulation buffer, formulation of final bulk, sterile filtration, aseptic filling, capping, and visual inspection process steps.

The SC FP manufacturing process consists of formulation of final bulk, sterile filtrations, aseptic filling and stoppering, and visual inspection process, to produce unassembled drug product (uDP) in a pre-filled syringe without plunger rod. uDP is further assembled into PFS-S or AI.

Control of critical steps and intermediates

CT-P47 IV and SC FP manufacturing processes are controlled by multiple controlled process parameters and in-process controls. The criticality of process variables (input and output variables) has been classified on the basis of a risk assessment. All Critical Process Parameters and Critical In-Process Controls (CIPC) have designated acceptance criteria, that have been set based on development studies and/or historical manufacturing data and process validation. The controlled parameters and in-process tests with their proposed limits/ranges were presented for all relevant manufacturing steps.

The hold times applied during CT-P47 IV FP manufacturing have been validated as part of the process validation. There are no hold times in CT-P47 SC manufacturing process. There are no intermediates in the CT-P47 IV or SC FP manufacturing processes.

Overall, the proposed control strategy seems adequate and can be agreed.

Process validation

IV FPs

The CT-P47 400mg and 200mg IV FP manufacturing processes were validated at the proposed commercial manufacturing site.

The validation studies covered all FP manufacturing steps i.e. preparation of formulation buffer, formulation of CT-P47 final bulk, filtration, sterile filtration, aseptic filling, capping, and visual inspection.

Several consecutive commercial scale CT-P47 FP lots, manufactured from AS originating from different AS batches were used in the studies. The CT-P47 80mg IV FP manufacturing process was validated at the proposed commercial manufacturing site. The validation studies covered all 80 mg FP

manufacturing steps i.e. preparation of formulation buffer, formulation of final bulk, sterile filtration, aseptic filling, capping, and visual inspection.

Maximum processing times and hold times were determined to establish acceptable limits for exposure to controlled room temperature during FP manufacture. Consistency of product quality across the FP batch was evaluated against batch release acceptance criteria.

In addition, validation activities covered filter validation for the sterilising filters using worst case filter conditions established by risk assessment. Overall, adequate data of filter validation was presented, and it is considered acceptable.

SC FP

The CT-P47 SC FP manufacturing process was validated at the proposed commercial manufacturing site, using several consecutive commercial scale CT-P47 FP lots. The validation studies covered all FP manufacturing steps to produce the uDP. Once CT-P47 SC FP has been manufactured as uDP, it is further assembled into PFS-S or AI. In addition, validation activities covered filter validation.

Overall, the CT-P47 IV (400mg, 200mg, and 80mg) and SC (162mg) FP manufacturing processes have been appropriately validated. All pre-determined acceptance criteria were satisfactorily met for all evaluated parameters, in-process controls and release tests.

2.4.3.3. Product specification

Specification and justification of specification

The proposed commercial IV and SC FP release and shelf-life specifications have been provided. The proposed specifications include general tests, safety tests, identity test, purity/impurity tests, content, potency tests and functionality tests for the SC FP.

Overall, the proposed CT-P47 FP specifications are considered appropriate and in line with current guidance.

Characterisation of impurities

No additional impurities are detected in the CT-P47 FP compared to the AS.

Elemental impurities have been evaluated in accordance with ICH Q3D in CT-P47 IV and SC. The elemental impurity studies demonstrate an extremely low risk from elemental impurities.

The CT-P47 FP manufacturing processes were also assessed with respect to the risk of the presence of nitrosamine impurities. An adequately detailed risk assessment was performed and confirms that there is no risk of nitrosamine impurities present in CT-P47 FPs.

Analytical procedures

CT-P47 SC and IV FPs are tested using a combination of compendial and non-compendial methods.

Analytical methods have been adequately described. Compendial analytical methods are performed in accordance with the relevant Ph. Eur. monographs.

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

The analytical procedures have been appropriately validated in accordance with ICH Q2(R1). Verification data has been presented for all the compendial methods and the data presented shows

that all the verification results met the acceptance criteria, and the methods are considered appropriate for their intended use.

Batch analysis

Batch analyses data are presented for several CT-P47 (IV) and (SC) FP batches. All batches were released as per the specification in place at the time of release. All results comply with the proposed commercial specifications.

Container closure

Detailed technical drawings and critical dimensions are provided for all components of the container closure systems. The container closure system for CT-P47 (IV) FP is composed of vial, stopper and seal as primary packaging components. The vial and stopper meet both Ph. Eur. and USP and requirements.

The primary container closure system used for CT-P47 (SC) FP is a 1 mL Type I glass syringe with a ½ inch (1.27 cm) fixed (staked-in) needle (26G thin wall for PFS-S and AI). The syringe is closed with a siliconised elastomeric plunger stopper and a needle shield. The glass syringe, plunger stopper, and rigid needle shield meet both Ph. Eur. and USP and requirements.

Overall, the container closure systems for CT-P47 FPs have been presented appropriately and in sufficient detail. The applicant has confirmed that the sterilisation of the primary container is in line with EMA/CHMP/QWP/ 850374/2015. Notified Body Opinions indicating PFS-S and AI compliance with the General Safety and Performance Requirements (GSPRs) were initially missing (Major Objections) and have been adequately provided.

The information provided is sufficient and adequate.

2.4.3.4. Stability of the product

A shelf life of 24 months when stored at 2°C - 8°C is claimed for the finished product (IV) for the unopened vial.

A shelf life of 36 months when stored at 2°C - 8°C is claimed for the finished product (SC) in PFS/PFP.

The applicant has provided data on CT-P47 FP stability studies performed at the long-term storage condition, for CT-P47 IV and CT-P47 SC at the accelerated storage condition, and at the stress storage conditions.

All test methods used for stability testing are performed as described in CTD Sections 3.2.P.5.2. Stability study protocols have been provided for all presentations and conditions.

The proposed shelf-life of CT-P47 (IV) 400mg, 200mg, and 80 mg FP is 24 months at 2°C - 8°C. If necessary, the diluted infusion solution with 0.9% sodium chloride injection or 0.45% sodium chloride injection may be kept at refrigerated condition for up to 1 month or room temperature up to 30 °C for up to 48 hours.

The proposed shelf-life of CT-P47 (SC) PFS-S and AI is 36 months when stored at 2°C - 8°C. The product may be stored at temperatures up to a maximum of 30°C for a period of up to 21 days.

The provided stability data supports the proposed shelf-life for CT-P47 IV and SC FPs.

In-use stability for IV FP

In-use stability studies for IV FP have been performed at long-term condition with subsequent incubation at accelerated condition.

After dilution, the prepared solution for infusion is physically and chemically stable in sodium chloride 9 mg/mL (0.9%) or 4.5 mg/mL (0.45%) solution for injection.

The currently available data supports storage of the diluted product for 48 hours at 30°C and for up to 1 month at 2°C - 8°C.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C–8°C, unless dilution has taken place in controlled and validated aseptic conditions.

To mimic the administration procedure, filtration of the diluted CT-P47 FP through infusion line and inline filter was studied. The data showed no change in quality attributes after using the infusion set with an in-line filter.

Photostability

To assess the sensitivity of CT-P47 FP to light, IV CT-P47 FP (representing the worst case of CT-P47 vial to light exposure), and SC FP was subjected to photostability testing. The results indicate that CT-P47 FP is photo-stable and adequately protected from exposure to light when stored in its secondary packaging.

2.4.3.5. Biosimilarity

CT-P47 has been developed as a biosimilar to EU-RoActemra (tocilizumab). A comprehensive analytical biosimilarity exercise has been performed according to the current guidance of CHMP/437/04 Rev 1 and EMA/CHMP/BWP/247713/2012.

Both CT-P47 and EU-RoActemra are provided in SC (PFS, 180 mg/mL) and IV (vial, 20 mg/mL) presentations. A 2-way analytical comparability study was performed separately for SC and IV presentations. Analytical similarity was assessed in a comprehensive similarity exercise using EU-sourced RoActemra as reference medicinal product (RMP). The comparability assessment was conducted as per the relevant EU guidelines on the development of similar biological medicinal products (CHMP/437/04 Rev 1, EMA/CHMP/BWP/247713/2012), as well as the principles of comparability as per ICH Q5E.

In conclusion, the selection of CT-P47 and EU-RoActemra SC/IV batches is deemed appropriate ensuring sufficient batch-to-batch variability for biosimilarity evaluation.

Biosimilarity approach

Discussion on the QTPP and identification of critical QAs has been described in the CTD section 3.2.S.2.4.1, which is deemed sufficient.

Statistical analysis was not applied for physicochemical attributes. Instead, the mean and SD as well as the spread of the underlying distribution from quantitative analyses were compared and any differences were discussed and justified in terms of the potential impact on clinical efficacy, PK, safety and immunogenicity. Additionally, primary data (such as spectra and chromatograms) for each batch as well as summary tables for each QA were provided allowing assessment of the biosimilarity data. Therefore, the approach is considered agreeable.

The similarity ranges were established for key biological assays. A quality range (QR) was set. A comprehensive set of state-of-the-art orthogonal methods were used to compare the primary and higher order structures, post-translational modifications (PTMs), charged variants, glycan structures, purity and impurities, protein concentration, and biological activity of Fab and Fc related functions.

Additional characterisation studies, including e.g. demonstration of lack of ADCC and CDC activity and comparison of forced degradation profiles were performed. In general, relevant quality attributes of tocilizumab were appropriately evaluated in the biosimilarity exercise.

In conclusion, methods used for biosimilarity assessment are considered scientifically sound, appropriately qualified and suitable for the intended use.

Based on the presented data the applicant´s approach to demonstrate biosimilarity is considered appropriate. **Table 1** below includes a summary of the biosimilarity assessment including a critical evaluation of biosimilarity.

Table 1. Summary of biosimilarity assessment

Molecular parameter	**Attribute**	**Methods**	**Key findings, conclusions**
Primary structure and PTMs	Intact mass	LC-MS (reduced and non-reduced)	The observed reduced and non-reduced intact masses for light chain and deglycosylated heavy chain and for glycosylated species were highly similar.
	Primary sequence of HC and LC	Peptide mapping by LC-MS (after Trypsin and Asp-N digestion)	Identical primary sequence with sequence coverage of 100%. The amino acid sequences were confirmed by MS/MS analysis.
	Deamidation		Deamidation levels in CT-P47 were slightly lower than in EU-RoActemra. Observed minor differences are not considered clinically relevant.
	Oxidation		Similar low level of methionine oxidation.
	Heavy chain N/C-terminal variants		The level of HC N-terminal pyroglutamate was similar in both IV products and in CT-P47 SC, whereas EU-RoActemra SC had slightly lower level of pyroglutamate. Minor difference is not clinically significant. CT-P47 has higher level of HC C-terminal lysine variant than EU-RoActemra, which is considered clinically insignificant.
Charged variants	Isoelectric point, pI	icIEF	Five peaks with highly similar pI values were identified in both products.
	Charged variants	IEC-HPLC	The same number of peaks were identified in both products with some differences in the peak ratios. Acidic variants: lower in CT-P47 due to lower level of deamidation and sialylation Basic variants: higher in CT-P47 due to higher level of C-terminal lysine The main peak was similar in both SC products and in CT-P47 IV, whereas EU-RoActemra IV had higher main peak due to lower level of basic variants. The observed differences in charge variant profiles are unlikely to have clinically meaningful impact.
Glycation & glycosylation	Glycation	LC-MS after deglycosylation and reduction	CT-P47 had higher level of glycation in both LC and HC. Data has been presented indicating that the potential glycation sites are not involved in antigen binding.
	Oligosaccharide profiling	HILIC-UPLC	The oligosaccharide profile is conserved between the two products. The overall level of fucosylated, afucosylated and high mannose glycans were comparable. Galactosylation: lower in CT-P47

Molecular parameter	Attribute	Methods	Key findings, conclusions
			Lower galactosylation level was reflected in lower Fcγ receptor binding, but since tocilizumab does not have Fc effector functions, differences are not considered clinically relevant. Sialylation: lower in CT-P47 Overall level of sialylation is low (in both products), and the observed small difference is not considered clinically meaningful.
	N-linked glycan analysis	LC-MS	G0F and G1F are the main N-glycan structures in both products. Only N-acetyl neuraminic acid (NANA) was detected in sialylated glycans. Minor differences in N-glycans are not expected to have clinical impact.
Purity / Impurity	Monomer, HMW, LMW	SEC-HPLC	**SC:** The mean values for monomers, HMW and LMW were comparable between CT-P47 and EU-RoActemra, whereas the ranges were wider for CT-P47. The observed small differences are not considered clinically meaningful. **IV** products had comparable purity/impurity profile.
	Monomer content, molecular weight	SEC-MALS	The molecular weight and content of monomers, HWM and LMW species were similar.
	Aggregate content, monomeric purity	AUC	
	Intact IgG and impurity	Non-reduced CE-SDS	CT-P47 had lower intact IgG level and correspondingly higher impurity level than the RMP. Observed difference is considered small and unlikely to adversely impact on clinical safety and efficacy.
	LC+HC and non-glycosylated HC (NGHC)	Reduced CE-SDS	Comparable level of purity and NGHC in both products.
Higher order structure	Secondary and tertiary structures	Circular dichroism (CD)	Similar secondary and tertiary structures as well as thermal stabilities.
	Thermal stability, thermal transition temperatures	Differential scanning calorimetry (DSC)	
	Secondary structure	Fourier transform infrared spectroscopy (FTIR)	
	Free thiols	DTNB/Ellman's assay	CT-P47 has slightly higher level of free thiols, which is unlikely to have clinical impact.
	Disulphide bonds	Non-reduced peptide mapping	Similar disulphide bonds.
Content	Protein concentration	UV_{280nm} by SoloVPE	Similar protein concentration (SC 180 mg/mL. IV 20 mg/mL).
Fab binding related biological activity	Soluble IL-6R binding	ELISA	Fab binding and functional assays demonstrate high similarity.
	Membrane bound IL-6R binding	Cell-based binding assay (CELISA)	
	Inhibition of IL-6 mediated cell proliferation	DS-1 cell line expressing mIL-6R	

Molecular parameter	Attribute	Methods	Key findings, conclusions
	Competition of IL-6 and tocilizumab binding to IL-6R	ELISA	
	Dissociation of IL-6 from IL-6/sIL-6R complex by tocilizumab	ELISA	
	Inhibition of IL-6 induced activation of JAK-STAT pathway	IL-6 reporter inhibition assay using HEK-Blue™ IL-6 cells	Additional mode-of-action study indicates similar downstream effect of IL-6R binding.
Fc binding related biological activity	C1q binding	ELISA	Similar C1q binding
	FcγRIIIa (V/F-type), FcγRIIIb, FcγRIIa, FcγRIIb, and FcγRIa Binding	SPR	CT-P47 has lower binding to FcγRIIIa (V/F-type) and FcγRIIIb mainly due to lower galactosylation level. However, the KD values were in the same order of magnitude for both products. As ADCC and CDC activities are not relevant for the MoA of tocilizumab, differences are not considered clinically relevant. FcγRIIa, FcγRIIb, FcγRIa: similar binding
	FcRn binding	SPR	Similar FcRn binding with SC products. FcRn binding is considered similar between the two products, and the small difference in IV presentations is unlikely to be clinically meaningful.
	ADCC and CDC activity	ADCC: DS-1 and PBMCs CDC: DS-1 cells	Similar lack of ADCC and CDC activities.
Forced degradation	High temperature (55 ± 5 °C)	UV_{280nm} SoloVPE, LC-MS, IEC-HPLC, SEC-HPLC, r/nr CE-SDS, SPR (FcRn), sIL-6R ELISA, Inhibition of IL-6-mediated cell proliferation	**SC:** The degradation profiles were mostly similar between CT-P47, EU-RoActemra and US-Actemra. However, (Ro)Actemra was more susceptible for oxidation due to lower methionine content. **IV:** Due to the different formulation (no methionine in RMP) more pronounced changed were observed in several QAs of (Ro)Actemra. After buffer exchange all three IV products were similarly impacted by stress conditions. The presented degradation profiles support the claim for biosimilarity.
	Chemical oxidation (0.03-0.06% H_2O_2)		
	Photostability (UV light)		
	Low/high pH		Similar degradation profiles.
Thermal stability	Accelerated stability (25±2°C/60±5% RH)	Same methods as for forced degradation studies	Accelerated and stressed stability data demonstrate broadly similar stability trends and degradation profiles supporting the biosimilarity claim.
	Stressed stability (40±2°C/75±5% RH)		

Summary

Similarity between CT-P47 and EU-RoActemra has been demonstrated for the following physicochemical and biological properties:

- Primary structure and post-translational modifications
- Charged variants
- Glycosylation

- Purity/impurity
- Higher order structure
- Content (protein concentration)
- Thermal stability and degradation studies
- Biological activity:
  - sIL-6R binding
  - mIL-6R binding
  - Inhibition of IL-6 mediated cell proliferation
  - Competition of IL-6 and tocilizumab binding to IL-6R
  - Dissociation of IL-6 from IL-6/sIL-6R complex by tocilizumab
  - Inhibitory activity on IL-6 induced JAK-STAT pathway
  - C1q Binding
  - FcγRIIa, FcγRIIb, and FcγRIa binding
  - FcRn binding
  - Lack of ADCC and CDC activity

The totality of the presented physicochemical and biological data supports the biosimilarity for CT-P47 and EU-RoActemra. Primary and higher order structures were shown to be broadly similar, with some differences in C-terminal lysine variants, charge variants, glycosylation and minor differences in glycation and purity/impurity profiles. Observed differences were appropriately discussed and shown not to be clinically meaningful, as all biological activities relevant to the MoA (sIL-6R and mIL-6R binding, inhibition of IL-6 mediated cell proliferation, competition of IL-6 and tocilizumab binding to IL-6R, dissociation of IL-6 from IL-6/sIL-6R complex by tocilizumab, and inhibitory activity on IL-6 induced downstream pathway) were similar between CT-P47 and EU-RoActemra.

Comparable binding was demonstrated to C1q and Fcγ receptors, except binding to FcγIIIa (V-type, F-type) and FcγIIIb receptors was lower due to overall lower galactosylation level of CT-P47. However, as Fc receptor functions do not play a role in the MoA of tocilizumab, which was appropriately demonstrated by similar lack of ADCC and CDC activity for both products, observed differences do not preclude the similarity claim. FcRn binding was generally comparable between CT-P47 and EU-RoActemra, and the small difference observed in IV presentations is highly unlikely to be clinically meaningful. The control strategy is adequately established to ensure consistent FcRn binding of CT-P47 batches during commercial manufacturing.

Overall, the presented comparative quality data support the biosimilarity between CT-P47 and EU-RoActemra. Observed differences are adequately discussed and appropriately justified being unlikely to have any clinically meaningful impact on PK, efficacy, or safety.

2.4.3.6. Adventitious agents

No human origin raw materials were used in the generation of MCB or during the manufacturing process of CT-P47. However, some animal derived raw materials were used. Appropriate TSE risk assessments were provided for all animal derived raw materials. Overall, it is agreed that TSE associated risk with CT-P47 is negligible.

The risk of microbial and mycoplasma contamination has overall been adequately addressed.

Cell banks were extensively characterised for both endogenous viruses and adventitious viral contamination. The unprocessed bulk harvests were tested for viruses. The choice of viruses is endorsed.

Scale-down models of the commercial purification process were employed to evaluate the ability of specific processing steps to remove and/or inactivate potential viral contaminants. The scale-down model was considered to represent the production process closely enough. The methods used in the viral clearance studies have been appropriately validated/qualified.

The viral clearance studies were performed in accordance with ICH Q5A guideline and demonstrate adequate capacity of the production process to inactivate or remove viruses.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Avtozma (CT-P47) is developed as a tocilizumab biosimilar to the reference medicinal product EU-RoActemra. Overall, Module 3 of the CT-P47 dossier is of good quality and all issues raised during the assessment of the dossier, including the Major Objections related to GMP certificate and Notified Body Opinions, have been appropriately addressed by the applicant.

The manufacturing processes for the active substance and final product reflect a standard manufacture of monoclonal antibody products. Valid proof of GMP compliance has been provided for all AS and FP manufacturing and testing sites.

The AS and FP manufacturing processes, process controls, process development and process validations as well as raw and starting materials used for the manufacture have been appropriately described. The data support the conclusion that the manufacturing process reliably generates active substance and finished product meeting their predetermined specifications and quality attributes.

Comprehensive panels of release specifications are set for CT-P47 AS and FP.

The proposed AS shelf life when stored at long-term condition, and the proposed FP shelf-life of 24 months for IV presentations (400mg, 200mg, 80 mg) and 36 months for SC presentations (PFS-S, AI) when stored at 5±3°C are acceptable and supported by long-term stability data.

CT-P47 FP (SC presentation) can be administered using 2 types of device presentations: pre-filled syringe with safety guard and auto-injector. CT-P47 FP (SC) is a drug-device combination product, where the medicinal product provides the primary mode of action and the single-use device components, and medicinal product form a single integral product. Notified Body Opinions indicating the pre-filled syringe and auto-injector compliance with the GSPRs have been provided.

A comprehensive assessment of biosimilarity between CT-P47 and EU-RoActemra (SC and IV presentations) has been presented. Observed differences are adequately discussed and justified not being clinically meaningful. Overall, the presented quality data support the biosimilarity of CT-P47 and EU-RoActemra.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

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

2.4.6. 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.

2.5. Non-clinical aspects

2.5.1. Introduction

The nonclinical data to support the biosimilarity claim of CT-P47 and EU-RoActemra (tocilizumab) relies on a battery of *in vitro* pharmacodynamic studies, which have been performed as part of the CMC program assessment. Therefore, these studies are shortly summarised under the nonclinical section to avoid repeating the data.

In addition, a supportive *in vivo* GLP-compliant 4-week repeat-dose toxicity study with toxicokinetics (TK) assessment was performed in cynomolgus monkeys (Study AA44AA).

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The results from intravenous (IV) formulation were similar to those of subcutaneous (SC) drug product (DP). The assays characterising the interactions with the key target, i.e. to sIL-6R and mIL-6R were determined comparing the CT-P47 to in-house primary reference standard. The batches used in these comparative assays are described under the Quality/biosimilarity assessment. In addition to tabulated results, the similar lack of ADCC and CDC activity was demonstrated for CT-P47 and EU-RoActemra.

2.5.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were conducted.

2.5.2.3. Safety pharmacology programme

No separate safety pharmacology studies were performed and are not required in line with the regulatory guidance for biosimilar development (EMA/CHMP/BMWP/403543/2010). Safety endpoints were incorporated into the 28-day repeat-dose toxicity study in cynomolgus monkeys. No significant differences were noted between CT-P47 and EU-RoActemra treated animals regarding the safety pharmacology.

2.5.2.4. Pharmacodynamic drug interactions

Not applicable.

2.5.3. Pharmacokinetics

No stand-alone pharmacokinetic studies were included and are not required for a biosimilar. A toxicokinetic analysis was performed as part of a repeat-dose toxicity study in cynomolgus monkeys and summarised under 2.5.4. Toxicology.

Detection of tocilizumab levels in cynomolgus monkey serum after exposure to CT-P47 was done with validated electroluminescence assay (ECLA).

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No single dose toxicity study was conducted and are not required for a biosimilar in line with the regulatory guidance for biosimilar development (EMA/CHMP/BMWP/403543/2010).

2.5.4.2. Repeat dose toxicity

A GLP-compliant 28-Day repeat-dose subcutaneous administration toxicity study (Study AA44AA) was performed in cynomolgus monkeys. The toxicity and TK profiles of CT-P47 (162 mg/0.9 mL PFS) and EU-RoActemra (162 mg/0.9 mL PFS) were compared. Monkeys (3/sex/group) received a 100 mg/kg dose once weekly via SC for 4 weeks.

There were no differences in the majority of toxicology endpoints between CT-P47 and EU-RoActemra. The differences noted were in the calcium levels, in the ALT, AST and creatinine kinase levels (increased in CT-P47 compared to EU-RoActemra treated animals) and in spleen (increased in CT-P47 compared to EU-RoActemra treated animals), pituitary and uterine weights (decreased in CT-P47 compared to EU-RoActemra treated animals) relative to the body weights. These differences were concluded as incidental and not of a toxicological concern.

The increase in mean levels of ALT, AST and creatinine levels in CT-P47 group was due to increase in 1 out of 3 female animals treated. No alterations were observed in tissues or organs attributable to the finding, and therefore these increases are considered not toxicologically relevant.

2.5.4.3. Genotoxicity

Not applicable.

2.5.4.4. Carcinogenicity

Not applicable.

2.5.4.5. Reproductive and developmental toxicity

Not applicable.

2.5.4.6. Toxicokinetic data

A toxicokinetic analysis was performed in cynomolgus monkeys as part of a repeat-dose toxicity study with CT-P47 and EU-RoActemra dose of 100 mg/kg (Study AA44AA). Systemic exposure to CT-P47 and EU-RoActemra was independent of sex. $AUC_{0\text{-}168}$ and C_{max} were between two- and three-fold greater on Day 22 than on Day 1 with ratios ranging from 1.9 to 3.0 for CT-P47 and from 2.0 to 2.7 for EU-RoActemra, after repeated administrations. CT-P47 and EU-RoActemra showed similar toxicokinetics with slightly lower exposure (in terms of AUC_t and C_{max}) in CT-P47 group animals than EU-RoActemra with ratios ranging from 0.8 to 0.9.

Table 2 Mean CT-P47 or EU-RoActemra toxicokinetic parameters in monkey serum

Interval	Dose Level	Parameters	CT-P47		RoActemra	
(Day)	(mg/kg)		Male (n=3)	Female (n=3)	Male (n=3)	Female (n=3)
1	100	T_{max} (h)[#]	72	72	72	96
		AUC_{0-168} (µg*h/mL)	93707	86559	119223	111004
		combined M+F	*90133*		*115114*	
		C_{max} (µg/mL)	717	653	861	850
		combined M+F	*685*		*856*	
22	100	T_{max} (h)[#]	72	72	48	72
		AUC_{0-168} (µg*h/mL)	230129	243996	281504	260271
		combined M+F	*237062*		*270888*	
		C_{max} (µg/mL)	1587	1704	1986	2020
		combined M+F	*1644*		*2003*	

2.5.4.7. Local tolerance

Local tolerance for repeated SC injection of CT-P47 (SC formulation, 162 mg/0,9 ml PFS) was assessed as part of the 4 week repeat-dose toxicity study in cynomolgus monkeys. There were no toxicologically significant differences in injection site findings between the animals administered either CT-P47 or EU-RoActemra.

2.5.4.8. Other toxicity studies

No other toxicity studies have been conducted.

2.5.5. 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, tocilizumab is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

Pharmacodynamics

The demonstration of biosimilarity of CT-P47 and EU-RoActemra was focusing on the battery of receptor-binding studies or cell-based *in vitro* assays. No comparative *in vivo* pharmacodynamic studies were conducted and are not required.

The *in vitro* studies performed with CT-P47 and EU-RoActemra for both SC and IV formulations to demonstrate functional biosimilarity were adequate. Relevant guidelines for biosimilar medicinal products were followed. It was stated that the 3R principles were followed, however one toxicity study in cynomolgus monkeys was conducted which is not in line with these principles.

The results from *in vitro* functional analyses were presented as relative potency or binding (%) from key biological assays (Fab-binding related assays and FcRn binding) and were subjected to statistical analysis. Results indicated that CT-P47 and EU-RoActemra were similar in their functional activities

(100% of the CT-P47 data points fell within the quality range of EU-RoActemra). The binding to soluble and membrane bound IL-6R, inhibition of IL-6-mediated cell proliferation, competition of IL-6 and tocilizumab binding to IL-6R, and dissociation of IL-6 from IL-6/sIL-6R complex by tocilizumab were similar. In addition, CT-P47 and EU-RoActemra showed comparable binding to C1q and Fcγ receptors I, IIa, and IIb.

Differences were seen in binding affinities to FcγRIII. CT-P47 had lower binding affinity to FcγRIIIa V-type (81-112% vs. 109-118% EU-RoActemra), FcγRIIIa F-type and FcγRIIIb (87-107% vs. 104-112%). These differences were clarified by the applicant to result from lower level of total galactosylation in CT-P47 compared to that of EU-RoActemra. This rationale is acceptable. Considering that tocilizumab is unlikely to mediate Fc-effector functions, such as ADCC and CDC, the differences in binding to FcγRIIIs are not considered clinically relevant and impact efficacy, PK or safety. The similar lack of ADCC ad CDC activities was demonstrated for CT-P47 and EU-RoActemra. It has also been reported that altered FcγRIIIa binding affinity does not affect PK.

The formulation of CT-P47 differing slightly from that of EU-RoActemra (in excipients which are clinically inactive components) did not have an impact on the biological activities.

In conclusion, the similar functional activities for CT-P47 and EU-RoActemra have been adequately demonstrated. The observed differences in FcγRIIIs binding are appropriately justified raising no concerns on the biosimilarity of CT-P47 and EU-RoActemra.

No secondary pharmacology and pharmacodynamic interactions studies were conducted with CT-P47 and EU-RoActemra and are not required for a biosimilar. No differences in the safety pharmacology endpoints were seen between the CT-P47 and EU-RoActemra treated animals in the supportive 4-week repeat-dose toxicity study in cynomolgus monkeys.

Pharmacokinetics

Toxicokinetic analyses were conducted after 28-days repeat-dose study with CT-P47 and EU-RoActemra in the cynomolgus monkeys. No confirmatory dose analysis was done in the toxicology study, since the DPs were ready to use. The exposures were slightly lower in CT-P47-treated than in EU-RoActemra-treated animals. C_{max} at D1 and D22 were 80-82% and AUC_t 78% (D1) to 88% (D28) of those of RMP. There is no apparent explanation for the exposure differences. Due to the small scale of the study (n=3 in each group) and relative minor differences in the male and female combined mean exposure values, this is not considered to jeopardise the biosimilarity claim. Furthermore, and importantly, no differences were reported in the *in vitro* functional parameters that would indicate the possible effects in the PK.

As a conclusion, the slightly differing exposures in the CT-P47 and EU-RoActemra group animals are not considered critical for the biosimilarity claim.

Toxicology

The rationale to conduct the toxicology-TK study was not clear. CT-P47 and RMP were functionally similar *in vitro*, and differences noted in the FcγRIII binding affinities are not of a clinical relevance in terms of pharmacokinetics and safety. It was stated that 3R-principles were considered, but the conducting the toxicity study was not in line with these principles.

Majority of the toxicological endpoints analysed were similar in CT-P47 and EU-RoActemra. The small differences were noted in calcium levels, ALT, AST and creatinine kinase levels and in spleen, pituitary and uterine weights. The increases of liver enzyme mean values noted in the CT-P47 monkeys was originated from one female, which had 4.4-fold, 8.6-fold and 32-fold increases in ALT, AST and creatinine kinase levels, respectively, compared to the pretest values. None of these differences noted

were significant or would indicate differences in the toxicological characteristics of CT-P47 and EU-RoActemra. Local tolerance was assessed as part of the 4-week repeat dose toxicity study. There were no toxicologically significant differences in injection site findings between the animals administered either CT-P47 DP or EU-RoActemra. The applicant investigated only the subcutaneous formulation, CT-P47 DP (162 mg/0,9 ml PFS), which is acceptable considering that both CT-P47 SC and IV formulations were identical in their excipient content, differing only in concentration of polysorbate (0.02% vs. 0.05% in SC and IV formulation, respectively).

No single-dose toxicity, genotoxicity, carcinogenicity or developmental and reproductive toxicology studies were conducted and are not required for a biosimilar.

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-P47 (tocilizumab) is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Overall, the similar functional activities relevant for the Fab interactions with the key target i.e. sIL-6R and mIL-6R, and Fc-related characteristics for CT-P47 and EU-RoActemra has been adequately demonstrated.

The repeated dose cynomolgus monkey study of CT-P47 and EU-RoActemra supported the notion of lack of significant clinically relevant differences in toxicokinetic and toxicity characteristics.

The SmPC, section 5.3. is in line with the originator's SmPC.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Table 3 The phase 1 and phase 3 clinical studies to support the marketing authorisation of CT-P47

Study identifier	Study design	Population (incl. number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
CT-P47 1.1	Phase 1, randomised, double-blind, two-arm, parallel group,	Part 1: Randomised: 29 CT-P47: 14 EU-RoActemra: 15 Part 2:	CT-P47 PFS or EU-RoActemra PFS 162 mg/ 0.9 mL, a single SC injection via PFS	The primary PK endpoints: Part 2: $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}. The secondary PK endpoints:

	single-dose study in healthy subjects	Randomised: 289 220 males/ 69 females CT-P47: 146 EU-RoActemra: 143		Part 1: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, C_{max}, T_{max}, $t_{1/2}$, $\%AUC_{ext}$, λ_z, CL/F, and V_z/F. Part 2: T_{max}, $t_{1/2}$, $\%AUC_{ext}$, λ_z, CL/F, and V_z/F.
CT-P47 1.2	Phase 1, randomised, double-blind, three-arm, parallel group, single-dose study in healthy subjects	Randomised: 133 male subjects CT-P47: 45 EU-RoActemra: 44 US-Actemra: 44	CT-P47 IV, EU RoActemra IV or US Actemra IV 400 mg/20 mL, a single dose of 8 mg/kg as IV infusion	The primary PK endpoints: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max}. The secondary PK endpoints: T_{max}, $t_{1/2}$, $\%AUC_{ext}$, λ_z, CL/F, and V_z/F.
CT-P47 1.3	Phase 1, randomised, open-label, two-arm, parallel group, single-dose study in healthy subjects	Randomised: 314 216 males/ 99 females CT-P47 AI: 155 CT-P47 PFS: 159	CT-P47 AI or CT-P47 PFS 162 mg/ 0.9 mL, a single SC injection via AI or PFS	The primary PK endpoints: $AUC_{0\text{-}inf}$ and C_{max}. The secondary PK endpoints: $AUC_{0\text{-}last}$, T_{max}, $t_{1/2}$, $\%AUC_{ext}$, λ_z, CL/F, and V_z/F.
CT-P47 3.1	Phase 3, randomised, active-controlled, double-blind, two-arm, parallel group study in patients with moderate to severe active RA	Randomised: 471 RA patients CT-P47: 234 EU-RoActemra: 237	CT-P47 IV or EU-RoActemra IV 400 mg/20 mL, 8 mg/kg (not exceeding 800 mg/dose) by IV infusion Q4W, co-administered with MTX between 10 to 25 mg/week, oral or parenteral dose (dose and route must be maintained from beginning to end of the study) and folic acid (≥5 mg/week, oral dose)	Secondary PK endpoint: Trough serum tocilizumab concentration (C_{trough}) at each time point up to Week 52.
CT-P47 3.2	Single-arm, open-label, multiple-dose study to evaluate usability of SC AI of CT-P47 in patients with moderate to severe active RA	33	CT-P47 AI and PFS 162 mg/0.9 ml by SC injection via AI at Week 0 and Week 2 and then PFS EOW or weekly based on clinical response by investigator's discretion from Week 4 up to Week 10, in combination with MTX (between 10 to 25 mg/week, oral or parenteral dose) and folic acid (≥5 mg/week, oral dose)	-

2.6.2. Clinical pharmacology

The applicant has developed two formulations for the proposed biosimilar product, CT-P47, complying with the presentations available for the reference product RoActemra. The CT-P47 180 mg/ml solution for injection is intended for subcutaneous administration of 162 mg/0.9 ml dose in a prefilled syringe (PFS) or autoinjector (AI) and CT-P47 20 mg/ml concentrate for solution infusion available in vials containing 80 mg, 200 mg or 400 mg of CT-P47 for intravenous infusion of 4 mg/kg, 8 mg/kg, 10 mg/kg and 12 mg/kg doses. During the clinical development, two formulations have been used, i.e. 162 mg/0.9 ml in PFS or AI and 400 mg vial presentation of 20 mg/ml concentrate for solution for infusion. The same formulations of CT-P47 were used throughout the clinical development program.

Bioanalytical methods

Tocilizumab concentrations in human serum were determined by an MSD-ECL method with a quantitation range of 80.0-20000 ng/ml. The assay was validated using CT-P47, EU-RoActemra and US-Actemra. Haemolysed or lipemic matrix did not interfere with the assay. Bioanalytical reports including ISR were provided for studies 1.1 part one and two, 1.2, 1.3 and 3.1.

Anti-CT-P47 Antibodies in Human Serum were detected by an ECL method using HISDA approach. The samples were first screened using a human anti-tocilizumab positive control. Positive samples were then re-assayed in the presence of excess drug to confirm the result. Confirmed positive samples were titrated to evaluate the intensity of the concentration of ADA. The assay was fully validated according to current guidance and bioanalytical reports were provided. No target interference or effect from lipemic or haemolysed samples was observed. The drug tolerance was 60 µg/ml, well above the C_{trough} concentrations.

Neutralising antibodies were assayed by a competitive ligand binding assay. The choice of assay format was justified as the main mechanism of action of tocilizumab is IL-6R neutralisation and inhibition of IL-6R by tocilizumab is the most critical component of clinical efficacy for tocilizumab. The assay was validated according to EMA/CHMP/BMWP/86289/2010, Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use. Critical reagents were not formally qualified during assay development because a validated assay was not available at that point and the critical reagents were used based on assay performance. The validated assay was used for study 1.1 samples. Subsequently the assay sensitivity deteriorated, and the assay was partially re-validated to assess new cut points, LPC, and the PC acceptance criteria accordingly. The assay format, platform, critical reagent type, procedure, etc. were all the same except for the concentration of the critical reagent BT-IL-6. After the partial validation, the method was updated to TM.3175.04 to remove the PCM. The re-validated assay was used for study 1.2 and 1.3 samples. After the root cause was identified the originally validated assay was used for study 3.1 and 3.2 samples. Bioanalytical reports were provided.

During validation the high- and mid- positive controls did not meet the acceptance criteria for inter-assay precision (see discussion).

Each of these three analytical methods was developed by Syneos Health Laboratory.

2.6.2.1. Pharmacokinetics

Pharmacokinetic studies in healthy adult volunteers

Study CT-P47 1.1 – PK-equivalence study comparing SC injection (PFS) of CT-P47 and EU-RoActemra

Study sites and dates: The Part 1 was conducted in one study centre in South Korea between 05 Jan 2022 and 06 Apr 2022. The Part 2 of the study was conducted in seven study centres in South Korea. The first subject was randomised on 22 Dec 2021 and last subject visit was on 02 May 2022.

Study design: The study was a Phase 1, randomised, double-blind, two-arm, parallel group, single-dose study designed to compare the PK and safety of SC injection formulations of tocilizumab (CT-P47 and EU-approved RoActemra) in healthy subjects.

The study was conducted in two parts: Part 1 was conducted to compare preliminary safety and was planned to enrol 30 subjects; Part 2 was planned to enrol separately approximately 270 subjects to demonstrate PK similarity. The two parts were conducted and reported independent from each other.

Primary objective (Part 2) was to demonstrate PK similarity in terms of $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max} of CT-P47 and EU-approved RoActemra in healthy subjects up to Day 43.

Secondary objectives:

- Part 1: To evaluate safety in terms of treatment-emergent adverse events of CT-P47, compared to that of EU-approved RoActemra in healthy subjects up to Day 43
- Both Part 1 & Part 2: To evaluate additional PK, safety, and immunogenicity of CT-P47 and EU-approved RoActemra in healthy subjects up to Day 43

The subjects were randomised in 1:1 ratio to receive a single dose of CT-P47 or EU-approved RoActemra. Randomisation was stratified by body weight (<70 kg versus 70 kg to <90 kg versus ≥90 kg), gender (male versus female), and study centre (only for Part 2). A single dose (162 mg) of the study drug was administered in a double-blinded manner to the eligible subject's outer upper arm on Day 1.

Blood samples for PK analysis of tocilizumab were collected on Day 1 at pre-dose and 8 hours after the study drug administration, Days 2 (24 h), 3 (48 h), 4 (72 h), 5 (96 h), 6 (120 h), 7 (144 h), 8 (168 h), 10 (216 h), 13 (288 h), 16 (360 h), 19 (432 h), 22 (504 h), 29 (672 h), 36 (840 h) and the end-of study (EOS) visit on Day 43 (1008 h).

Blood samples for immunogenicity evaluation were collected on Day 1 at pre-dose and on Day 13 and at the EOS visit on Day 43.

Statistical methods: In Part 2 of the study, the statistical analysis of the natural log (ln)-transformed primary PK endpoints was done using an analysis of covariance model (ANCOVA) with treatment as fixed effect and stratification factors (body weight at Day -1, gender, and study centre) as covariates. The difference in least squares means between CT-P47 vs. EU-RoActemra and the associated 90% CIs were determined. Back transformation provided the ratio of geometric least square means and 90% CIs for these ratios. The similarity of PK between CT-P47 vs. EU-RoActemra was concluded if the 90% CIs for the ratios of geometric means of the comparison were entirely within the equivalence margin of 80% to 125% for $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}.

Part 1

The results of the Part 1 were reported separately from the Part 2. Overall, 29 subjects (26 males, 3 females) were randomised and received the study drugs (CT-P47 N=14; RoActemra N= 15). In total 28 subjects completed the study, as one subject withdrew from the study after receiving CT-P47.

The mean serum tocilizumab concentration-time profiles after SC administration of CT-P47 and EU-RoActemra to healthy volunteers in Part 1 are presented in **Figure 1**.

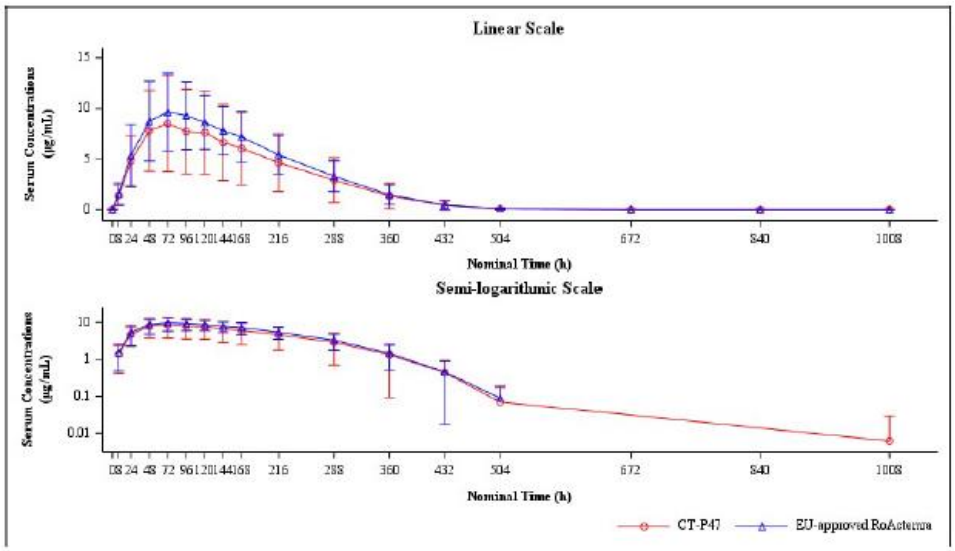


Figure 1 Mean (SD) serum concentrations of tocilizumab vs. time profiles on linear and semi-logarithmic scale in Part 1 (CT-P47 N=14; EU-RoActemra N=15).

Part 2

Interim analysis for sample size reassessment: An interim analysis was planned for sample size reassessment in the study protocol. After blinded review by the appointed independent data monitoring committee (IDMC), the sample size could be increased up to 478 subjects based on the actual drop-out rate and CV% of primary PK estimates ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}). The PK data up to 43 days from 150 subjects were included in the interim analysis. Based on the blinded review, the IDMC considered that increase of sample was not necessary.

Study subjects and withdrawals: In total, 289 subjects were randomised; 146 subjects in CT-P47 group and 143 in EU-RoActemra group (Intent-to-treat analysis set, ITT). Two subjects, who did not meet the inclusion/exclusion criteria but were randomised by mistake, were considered a major protocol deviation, and they were excluded from the ITT set. The baseline and demographic characteristics were comparable between the treatment groups for ITT set.

Finally, 144 subjects received one SC injection of CT-P47, and 140 subjects received EU-RoActemra and were included in the PK analysis set (N=284). Three subjects in both treatment arms discontinued the study after receiving study drug with 141 and 137 subjects completing the study successfully.

PK results / Part 2

Following subcutaneous injection of 162 mg single dose, the 90% CIs of the geometric mean ratios (CT-P47/EU-Roactemra) for the primary PK parameters were within the equivalence margins of 80% to 125% indicating similarity of PK between CT-P47 and EU-RoActemra (**Table 4**). The PK parameters and serum tocilizumab concentration-time profiles were comparable between the treatment arms

(**Tables 16-17 and Figure 2**). The median time to peak concentration T_{max} was approximately 4 days following CT-P47 and EU-RoActemra administration. After peak concentration, the serum tocilizumab concentrations decreased with mean $t_{1/2}$ mean of 1.646 days and 1.666 days for CT-P47 and EU-RoActemra, respectively. The relatively short $t_{1/2}$ can be explained by the fast non-linear target-mediated elimination of tocilizumab at low serum concentrations.

There were three subjects in CT-P47 group and one subject in EU-Roactemra group for whom the extrapolated-AUC % (%AUC_{ext}) was more than 20% of $AUC_{0\text{-}inf}$. The extrapolated AUC could not be determined for six subjects in CT-P47 group and for three subjects in EU-Roactemra group, thus, they were excluded from the primary PK analyses for $AUC_{0\text{-}inf}$ as defined in the SAP. In addition, there was one subject in EU-RoActemra group for which $AUC_{0\text{-}inf}$ could not be determined due to physiologically non-plausible plasma concentrations at late time-points.

Table 4 Summary of the ANCOVA analysis of the primary PK estimates for tocilizumab after administration of SC injection of CT-P47 or EU-RoActemra (PK-analysis set; CT-P47 1.1)

Treatment Comparison	PK Parameter (units)	Geometric LSM[a]		Ratio (%) of Geometric LSM[a]	90% CI[a]
		CT-P47	EU-approved RoActemra		
CT-P47 vs. EU-approved RoActemra	$AUC_{0\text{-}inf}$ (day·µg/mL)[b]	(n=138) 79.37	(n=136) 73.54	107.92	(98.04, 118.80)
	$AUC_{0\text{-}last}$ (day·µg/mL)[b]	(n=144) 77.55	(n=139) 72.52	106.93	(97.36, 117.43)
	C_{max} (µg/mL)	(n=144) 8.89	(n=140) 8.63	103.00	(94.67, 112.06)

Abbreviations: ANCOVA, analysis of covariance; $AUC_{0\text{-}inf}$, 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; LSM, least squared mean; PK, pharmacokinetic(s).

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

[a] The LSM differences and 90% confidence intervals for the differences were exponentiated to provide estimates of the ratio of adjusted geometric least square means (CT-P47/EU-approved RoActemra) and 90% confidence intervals for the ratios.

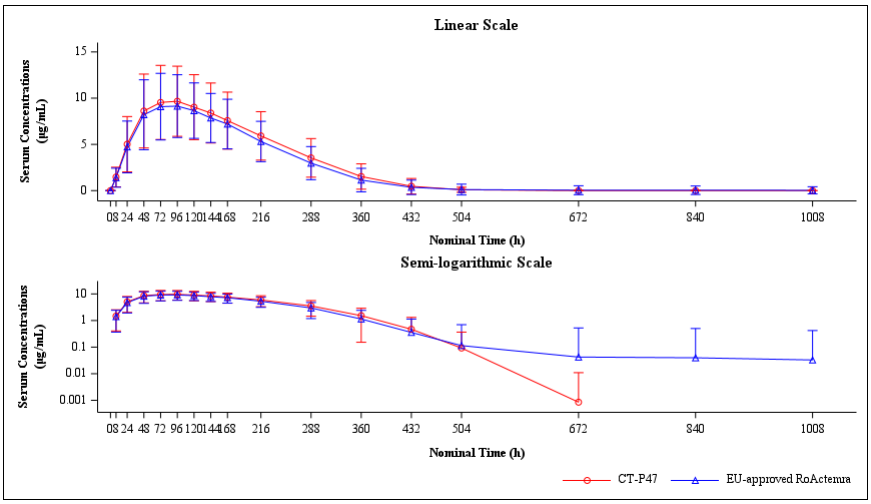


Figure 2 Mean (SD) serum concentrations of tocilizumab vs. time profiles on linear and semi-logarithmic scale in Part 2 (CT-P47 1.1)

Table 5 Primary PK-parameters for tocilizumab by treatment group (CT-P47 1.1)

PK Parameter (unit) Statistics	CT-P47 (N=144)	EU-approved RoActemra (N=140)
$AUC_{0\text{-}inf}$ (day·µg/mL)		
n	138	136
Mean (SD)	94.343 (40.9471)	85.983 (36.2279)
CV%	43.4022	42.1336
Geometric mean	83.452	78.182
Median	92.520	81.007
Minimum, Maximum	4.67, 216.24	11.03, 235.92
$AUC_{0\text{-}last}$ (day·µg/mL)		
n	144	139
Mean (SD)	92.568 (40.2780)	84.259 (35.4201)
CV%	43.5117	42.0373
Geometric mean	81.985	76.688
Median	89.165	79.430
Minimum, Maximum	4.33, 215.72	10.81, 235.71
C_{max} (µg/mL)		
n	144	140
Mean (SD)	10.33 (4.0131)	9.828 (3.5770)
CV%	38.848	36.395
Geometric mean	9.412	9.127
Median	10.20	9.515
Minimum, Maximum	0.892, 22.9	1.77, 19.9

Table 6 Secondary PK-parameters for tocilizumab by treatment group (CT-P47 1.1)

PK Parameter (unit) Statistics	CT-P47 (N=144)	EU-approved RoActemra (N=140)
T_{max} (day)		
n	144	140
Mean (SD)	3.824 (1.3059)	3.854 (1.2748)
CV%	34.1477	33.0727
Geometric mean	3.607	3.639
Median	3.989	3.989
Minimum, Maximum	1.00, 8.98	1.00, 6.99
$t_{1/2}$ (day)		
n	138	136
Mean (SD)	1.646 (0.67828)	1.666 (0.69780)
CV%	41.216	41.892
Geometric mean	1.569	1.581
Median	1.465	1.437
Minimum, Maximum	1.09, 6.39	1.05, 6.66
$\%AUC_{ext}$ (%)		
n	138	136
Mean (SD)	1.259 (4.2218)	1.294 (3.3311)
CV%	335.26	257.50
Geometric mean	0.4346	0.5042
Median	0.3247	0.4399
Minimum, Maximum	0.0951, 35.0	0.0911, 24.5
λ_z (1/day)		
n	138	136
Mean (SD)	0.4555 (0.096033)	0.4539 (0.10308)
CV%	21.085	22.708
Geometric mean	0.4417	0.4384
Median	0.4732	0.4822
Minimum, Maximum	0.108, 0.635	0.104, 0.658
CL/F (L/h)		
n	138	136
Mean (SD)	0.1020 (0.13254)	0.09874 (0.072807)
CV%	129.93	73.740
Geometric mean	0.08089	0.08634
Median	0.07296	0.08333
Minimum, Maximum	0.0312, 1.45	0.0286, 0.612
V_z/F (L)		
n	138	136
Mean (SD)	6.098 (11.413)	5.700 (4.9135)
CV%	187.16	86.207
Geometric mean	4.394	4.727
Median	3.802	4.376
Minimum, Maximum	1.50, 131	1.50, 38.7

Study CT-P47 1.2 – PK-equivalence study comparing IV infusion of CT-P47, EU-RoActemra and US-Actemra

Study sites and dates: The study was conducted in three study sites in Japan. The first subject was randomised on 20 Jan 2023 and last subject last visit was on 26 May 2023.

Study design:

The study was a Phase 1, randomised, double-blind, three-arm, parallel group, single-dose study designed to compare the PK and safety of intravenous (IV) infusion formulations of tocilizumab (CT-P47, EU-RoActemra, and US-Actemra) in healthy Japanese subjects.

Primary objective was to demonstrate PK similarity in terms of $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max} in pairwise comparisons of CT-P47, EU-RoActemra and US-Actemra when administered as IV infusion. Secondary objectives were to evaluate additional PK parameters, safety and immunogenicity of the treatments up to Day 56 after administration.

Healthy male and female subjects were randomised in a 1:1:1 ratio to receive one of the three treatments at Day 1. A balanced distribution among the treatment group ensured by randomisation stratified by body weight (<70 kg versus 70 kg to <90 kg versus ≥90 kg) and gender (male versus female). A single 8 mg/kg dose of CT-P47, EU-RoActemra, or US-Actemra was administered by a one-hour infusion to all eligible subjects on Day 1.

The blood samples for analysis of tocilizumab concentrations were collected pre-dose, end-of-infusion (EOI) (within 15 minutes after EOI), 1 hour after EOI, 2 hours after EOI, 6 hours after start of infusion (SOI), 12 hr, 24 hr, 48 hr, 72 hr, 168 hr, 336 hr, 480 hr, 648 hr, 816 hr, 984 hr, 1152 hr and 1320 hrs (Day 56, EOS) after SOI.

Blood samples for evaluation of immunogenicity were collected on baseline pre-dose and on Day 15 (360 hrs after SOI) and on Day 56 (1320 hrs after SOI) on EOS visit. Additional sample was collected in case of immune-related adverse event (e.g. hypersensitivity) occurred.

Statistical methods: The statistical analysis of the ln-transformed primary PK endpoints was done using an ANCOVA with treatment as fixed effect and with body weight at Day -1 as covariate. The similarity of PK between CT-P47 vs. EU-RoActemra, CT-P47 vs. US-Actemra, and EU-RoActemra vs. US-Actemra was concluded if the 90% CIs for the ratios of geometric means of the comparison were entirely within the equivalence margin of 80% to 125% for $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}.

Study subjects and withdrawals: In total 133 subjects (ITT set) were randomised to receive intravenous infusion of either CT-P47 (N=45), EU-RoActemra (N=44) or US-Actemra (N=44). The treatment arms were balanced with regards the main demographics (age, weight, height, BMI). The subjects were in median 63.9 kg (range 51.80-87.50 kg) in CT-P47 group, 61.6 kg (52.60-78.40 kg) in EU-RoActemra group and 61.55 kg (51.80-85.60 kg) in US-Actemra group. There were no subjects in the heaviest weight category, i.e. ≥ 90 kg. The body weight of the enrolled subjects was restricted to the upper limit of 100 kg considering that the doses of RoActemra should not exceed 800 mg.

One subject withdrew his consent before study drug administration in the EU-RoActemra group, thus, 45 subjects were administered CT-P47, 43 subjects received EU-RoActemra and 44 subjects received US-Actemra (PK-analysis set, N=132). One subject withdrew his consent 19 days after study drug administration in US-Actemra group. No major protocol deviations were reported.

PK results

Following IV infusion, the peak tocilizumab serum concentrations [mean (CV%) C_{max}] of 156.3 (12.398), 158.7 (12.977) and 161.0 (13.071) µg/mL were reached in median 2.0 hours, 1.08 hours,

and 2.0 hours in the CT-P47, EU-RoActemra and US-Actemra treatment groups, respectively (**Tables 8-9**). After peak concentration, the serum concentrations declined with mean $t_{1/2}$ of 116.8 (4.8 days), 121.4 (5.0 days), and 122.9 hours (5.1 days) for the CT-P47, EU-RoActemra, and US-Actemra treatment groups, respectively.

The ANCOVA analysis indicated, that mean total and peak systemic exposure to tocilizumab in terms of $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max} were similar between the 3 treatment groups following a single IV infusion of 8 mg/kg of tocilizumab in healthy subjects (

Table 7). The 90% CIs of the geometric LS mean ratios for the primary PK endpoints were within the predefined 80% to 125% equivalence margin in all three pairwise comparisons. All secondary PK parameters (T_{max}, $t_{1/2}$, λ_z, CL, V_z, and $\%AUC_{ext}$) and mean serum concentration of tocilizumab were comparable among the 3 treatment groups.

The extrapolated AUC% was less than 20% for all subjects in this study indicating sufficient long blood sampling period for calculation of $AUC_{0\text{-}inf}$. One subject in the EU-RoActemra treatment group was excluded from the $AUC_{0\text{-}inf}$ analysis and from the calculation of the elimination phase related PK parameters ($t_{1/2}$, $AUC_{ext}\%$, $AUC_{0\text{-}inf}$, CL and V_z) due to unexpectedly high serum concentration on the last time point.

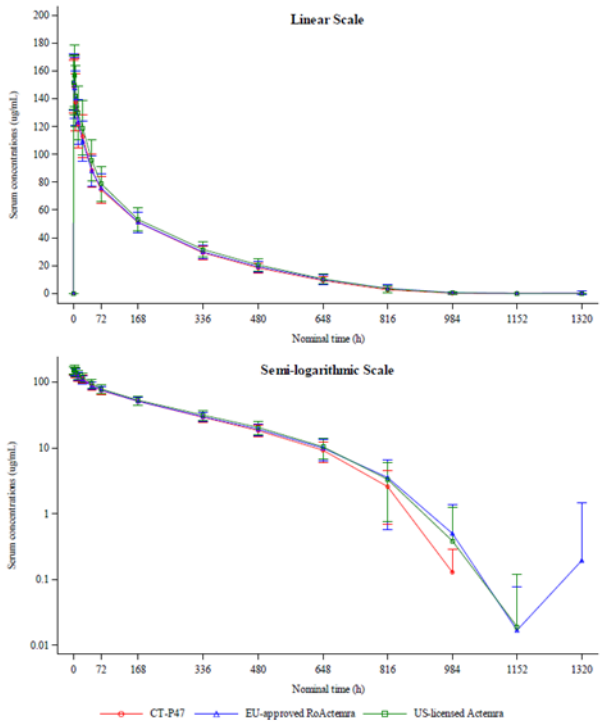


Figure 3 Mean (SD) serum tocilizumab concentrations-time curves on linear (upper panel) and semilogarithmic scale (lower panel) after intravenous infusion (CT-P47 1.2)

Table 7 Summary of the ANCOVA analysis of the primary PK estimates for tocilizumab after IV infusion of CT-P47, EU-RoActemra or US-Actemra (PK-analysis set; CT-P47 1.2)

PK Parameter (unit)	Comparison	Treatment	n	Geometric LS Means[a]	Ratio of Geometric LS Means (Test/Reference)[a]	90% CI[a]
$AUC_{0\text{-}inf}$ (hour·µg/mL)[b]	CT-P47	Test	45	26735.00	96.65	(92.09, 101.43)
	EU-approved RoActemra	Reference	42	27663.04		
	CT-P47	Test	45	26735.00	92.61	(88.30, 97.12)
	US-licensed Actemra	Reference	44	28869.86		
	EU-approved RoActemra	Test	42	27663.04	95.82	(91.30, 100.57)
	US-licensed Actemra	Reference	44	28869.86		
$AUC_{0\text{-}last}$ (hour·µg/mL)	CT-P47	Test	45	26637.45	96.41	(91.85, 101.19)
	EU-approved RoActemra	Reference	43	27630.43		
	CT-P47	Test	45	26637.45	92.99	(88.63, 97.57)
	US-licensed Actemra	Reference	44	28644.65		
	EU-approved RoActemra	Test	43	27630.43	96.46	(91.89, 101.25)
	US-licensed Actemra	Reference	44	28644.65		
C_{max} (µg/mL)	CT-P47	Test	45	154.15	97.51	(93.41, 101.79)
	EU-approved RoActemra	Reference	43	158.09		
	CT-P47	Test	45	154.15	96.44	(92.41, 100.64)
	US-licensed Actemra	Reference	44	159.84		
	EU-approved RoActemra	Test	43	158.09	98.90	(94.73, 103.25)
	US-licensed Actemra	Reference	44	159.84		

Table 8 Primary PK parameters for tocilizumab by treatment group (CT-P47 1.2)

PK parameter (unit) Statistic	CT-P47 (N=45)	EU-approved RoActemra (N=43)	US-licensed Actemra (N=44)
$AUC_{0\text{-}inf}$ (hour·µg/mL)			
n	45	42	44
Mean (SD)	27151.617 (3786.2931)	27760.810 (3764.2540)	29156.705 (4323.5220)
Median	27619.792	27481.201	28534.870
Minimum, Maximum	19524.42, 36593.39	21536.31, 36712.55	20250.44, 37525.54
CV%	13.9450	13.5596	14.8286
Geometric Mean	26896.272	27512.159	28843.015
$AUC_{0\text{-}last}$ (hour·µg/mL)			
n	45	43	44
Mean (SD)	27054.129 (3825.6464)	27750.049 (3750.5156)	28930.428 (4387.2699)
Median	27500.720	27357.102	28469.641
Minimum, Maximum	19507.53, 36549.57	21514.97, 36685.53	20236.61, 37476.10
CV%	14.1407	13.5153	15.1649
Geometric Mean	26792.293	27502.649	28604.638
C_{max} (µg/mL)			
n	45	43	44
Mean (SD)	156.3 (19.374)	158.7 (20.588)	161.0 (21.041)
Median	156.0	161.0	158.0
Minimum, Maximum	121, 200	118, 197	114, 196
CV%	12.398	12.977	13.071
Geometric Mean	155.1	157.3	159.6

Table 9 Secondary PK parameters by treatment group (CT-P47 1.2)

PK parameter (unit) Statistic	CT-P47 (N=45)	EU-approved RoActemra (N=43)	US-licensed Actemra (N=44)
T_{max} (hour)			
n	45	43	44
Mean (SD)	2.095 (1.1185)	1.782 (1.0087)	2.107 (0.9047)
Median	2.000	1.083	2.000
Minimum, Maximum	1.00, 6.00	1.00, 6.00	1.00, 6.00
CV%	53.3822	56.6018	42.9421
Geometric Mean	1.864	1.574	1.943
$t_{1/2}$ (hour)			
n	45	42	44
Mean (SD)	116.8 (31.890)	121.4 (34.312)	122.9 (30.569)
Median	127.9	125.5	126.2
Minimum, Maximum	43.1, 156	48.1, 172	47.8, 191
CV%	27.313	28.267	24.871
Geometric Mean	110.6	115.2	118.2
$\%AUC_{ext}$ (%)			
n	45	42	44
Mean (SD)	0.3847 (0.60873)	0.3619 (0.42680)	0.8021 (2.1325)
Median	0.1328	0.1820	0.1552
Minimum, Maximum	0.0188, 3.43	0.0184, 1.99	0.0227, 14.0
CV%	158.22	117.95	265.86
Geometric Mean	0.1717	0.1930	0.2454
λ_z (1/hour)			
n	45	42	44
Mean (SD)	0.006781 (0.0032665)	0.006455 (0.0028672)	0.006188 (0.0024633)
Median	0.005419	0.005523	0.005490
Minimum, Maximum	0.00445, 0.0161	0.00403, 0.0144	0.00363, 0.0145
CV%	48.173	44.418	39.810
Geometric Mean	0.006265	0.006015	0.005864
CL (mL/hour)			
n	45	42	44
Mean (SD)	19.31 (3.2891)	18.29 (2.7459)	17.65 (2.5723)
Median	19.50	18.31	17.47
Minimum, Maximum	13.4, 32.6	14.0, 28.0	12.9, 25.1
CV%	17.029	15.009	14.575
Geometric Mean	19.06	18.10	17.47
V_z (mL)			
n	45	42	44
Mean (SD)	3247 (999.16)	3190 (940.87)	3125 (832.38)
Median	3453	3354	3191
Minimum, Maximum	992, 4820	1070, 5050	1070, 4730
CV%	30.770	29.494	26.633
Geometric Mean	3043	3010	2980

Study CT-P47 1.3 – PK-equivalence study comparing SC injection of CT-P47 given with autoinjector (AI) or PFS

Study sites and dates: The study was conducted in four (4) study sites in South Korea. The first subject was randomised on 15 Nov 2022 and last subject last visit was on 24 Feb 2023.

Study design: The Phase 1, randomised, open-label, two-arm, parallel group, single-dose study was designed to compare the PK and safety of SC administration of CT-P47 AI and CT-P47 PFS in healthy subjects.

The primary objective of the study was to demonstrate PK similarity of the primary PK estimates $AUC_{0\text{-}inf}$ and C_{max} of CT-P47 SC administration by AI vs. PSF up to 43 days. Secondary PK parameters, safety and immunogenicity were compared as secondary objectives.

Subjects were randomised in 1:1 ratio to receive a single SC dose of 162 mg of CT-P47 administered either with an AI or a PFS. Subjects with a body weight of ≥60 and ≤100 kg for male and ≥50 and ≤100 kg for female and a BMI between 18.5 and 28.0 kg/m^2 (both inclusive) were planned to be enrolled. Randomisation was stratified by body weight (<70 kg versus 70 kg to <90 kg versus ≥90

kg), gender (male versus female), and study centre. The study drug was administered in the upper arm by a site-qualified and trained study personnel.

Blood samples for analysis of serum tocilizumab concentrations were collected on Day 1 Predose, Day 1 (8 hours after the administration of the study drug), Day 2 (24 hours), Days 3, 4, 5, 6, 7, 8, and 10 (48, 72, 96, 120, 144, 168 and 216 hours, respectively), Days 13, 16, 19, and 22 (288, 360, 432, and 504 hours, respectively), Days 29 and 36 (672 and 840 hours, respectively), and Day 43 (EOS; 1008 hours).

Samples for testing of immunogenicity were collected concomitantly with the PK samples pre-dose, on Day 13 and on Day 43 (EOS).

The parallel group, single dose study design and blood sampling schedule were similar to the previous SC study comparing the CT-P47 PFS formulation with EU-RoActemra (study CT-P47 1.1).

Statistical methods: The statistical analysis of the log-transformed primary PK endpoints was based on an ANCOVA model with treatment as fixed effect and body weight at Day -1 (if body weight measurement on Day -1 was not performed, body weight at screening visit was used), gender, and study centre as covariates. The similarity of PK between CT-P47 AI vs. CT-P47 PFS were concluded if the 90% CIs for the ratios of geometric means of the comparison were within the equivalence margin of 80% to 125% for $AUC_{0\text{-}inf}$ and C_{max}.

Study subjects and withdrawals: In total, 314 subjects were randomised to the two treatment arms: 155 subjects in the CT-P47 AI group and 159 in the CT-P47 PFS group (ITT set). Two subjects in both treatment arms withdrew consent before study drug administration, thus, finally 153 subjects received CT-P47 subcutaneously with an AI injection and 157 subjects with a PFS injection (PK-analysis set, N=310). In total 147 subjects completed the study in the CT-P47 AI group, and 153 subjects completed the study in in the CT-P47 PFS group after 6 subjects and 4 subjects had withdrawn consent during the study, respectively. Overall, demographic and baseline characteristics were similar between the treatment groups. No major protocol deviations were reported.

PK results

After SC injection of CT-P47, mean $AUC_{0\text{-}inf}$ and C_{max} of tocilizumab were comparable between the CT-P47 AI and CT-P47 PFS treatment groups (**Table 11**). Mean (±SD) serum concentration-time profiles of tocilizumab are presented in **Figure 4.** Median T_{max} occurred at 4.0 days and 3.0 days post-dose in CT-P47 AI and CT-P47 PFS treatment groups, respectively (**Table 12**). Mean $t_{1/2}$ was 1.6 days for both treatment groups. Mean $\%AUC_{ext}$, λz, CL/F, and V_z/F were comparable across both treatment groups.

In the ANCOVA analysis, the 90% CIs of the geometric LSM ratios for the primary PK endpoints were within the predefined 80.00% to 125.00% equivalence margin for each comparison, indicating PK similarity between CT-P47 AI and CT-P47 PFS **(Figure 4 Serum tocilizumab concentration vs. time profiles after CT-P47 injection by AI or PFS (CT-P47 1.3).**

Table *10*).

Extrapolated AUC was more than 20% for one subject in CT-P47 AI group and for two subjects in CT-P47 PFS group confirming the sufficient long blood sampling period in the study. In total, 13 subjects in the CT-P47 AI and 5 subjects in CT-P47 PFS group were excluded from the analysis of $AUC_{0\text{-}inf}$. and elimination phase related PK parameters as the PK parameters could not be reliably determined according to the SAP.

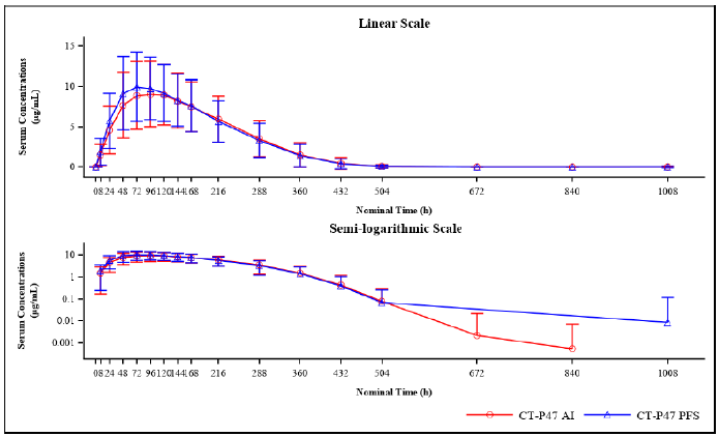


Figure 4 Serum tocilizumab concentration vs. time profiles after CT-P47 injection by AI or PFS (CT-P47 1.3).

Table 10 Summary of the ANCOVA analysis of the primary PK parameters for tocilizumab comparing CT-P47 given with an AI or a PFS (CT-P47 1.3)

Treatment Comparison	PK Parameter (units)	Geometric LSM[a]		Ratio (%) of Geometric LSM[a]	90% CI[a]
		CT-P47 AI	CT-P47 PFS		
CT-P47 AI vs. CT-P47 PFS	$AUC_{0\text{-}inf}$ (day·µg/mL)[b]	(n=140) 76.90	(n=152) 81.79	94.02	(85.87, 102.94)
	C_{max} (µg/mL)[c]	(n=150) 8.61	(n=157) 9.54	90.25	(82.98, 98.16)

Table 11 Primary PK parameters for tocilizumab by treatment (CT-P47 AI, CT-P47 PFS) (CT-P47 1.3)

PK Parameter (unit) Statistics	CT-P47 AI (N=153)	CT-P47 PFS (N=157)
$AUC_{0\text{-}inf}$ (day·µg/mL)[a]		
n	140	152
Mean (SD)	90.100 (43.3193)	93.625 (42.8708)
CV%	48.0793	45.7900
Geometric mean	79.852	83.222
Median	82.603	91.812
Minimum, Maximum	16.43, 255.11	12.02, 215.38
C_{max} (µg/mL)[b]		
n	150	157
Mean (SD)	9.823 (4.3747)	10.71 (4.3625)
CV%	44.537	40.749
Geometric mean	8.846	9.731
Median	9.435	10.60
Minimum, Maximum	2.19, 29.5	1.56, 27.6

Table 12 Secondary PK parameters for tocilizumab by treatment (CT-P47 AI, CT-P47 PFS) (CT-P47 1.3)

PK Parameter (unit) Statistics	CT-P47 AI (N=153)	CT-P47 PFS (N=157)
$AUC_{0\text{-last}}$ (day•μg/mL)[a]		
n	150	157
Mean (SD)	88.852 (43.5558)	92.129 (42.4655)
CV%	49.0207	46.0936
Geometric mean	77.813	81.611
Median	80.926	90.570
Minimum, Maximum	10.33, 246.91	11.75, 208.27
T_{max} (day)[a]		
n	150	157
Mean (SD)	4.174 (1.3421)	3.606 (1.2276)
CV%	32.1539	34.0405
Geometric mean	3.949	3.410
Median	4.000	3.019
Minimum, Maximum	1.00, 9.00	1.96, 7.00
$t_{1/2}$ (day)[b]		
n	140	152
Mean (SD)	1.581 (0.58258)	1.622 (0.72392)
CV%	36.854	44.635
Geometric mean	1.523	1.542
Median	1.427	1.451
Minimum, Maximum	1.03, 6.87	1.01, 7.51
$\%AUC_{ext}$ (%)[b]		
n	140	152
Mean (SD)	1.164 (5.9400)	1.130 (5.0248)
CV%	510.21	444.70
Geometric mean	0.4806	0.4299
Median	0.4034	0.3713
Minimum, Maximum	0.0963, 70.5	0.0854, 57.8
λ_z (1/day)		
n	140	152
Mean (SD)	0.4666 (0.092180)	0.4634 (0.097573)
CV%	19.756	21.056
Geometric mean	0.4551	0.4494
Median	0.4856	0.4779
Minimum, Maximum	0.101, 0.673	0.0923, 0.689
CL/F (L/h)[b]		
n	140	152
Mean (SD)	0.09742 (0.059952)	0.09440 (0.066234)
CV%	61.541	70.160
Geometric mean	0.08453	0.08111
Median	0.08172	0.07352
Minimum, Maximum	0.0265, 0.411	0.0313, 0.562
V_z/F (L)[b]		
n	140	152
Mean (SD)	5.447 (4.9262)	5.341 (4.8664)
CV%	90.436	91.117
Geometric mean	4.458	4.332
Median	4.209	3.976
Minimum, Maximum	1.30, 45.9	1.41, 42.5

Pharmacokinetics in the target population

<u>Study CT-P47 3.1 – Phase 3 study in patient with moderate to severe RA</u>

The study was designed to evaluate efficacy, PK and overall safety including immunogenicity of multiple doses of 8 mg/kg of either CT-P47 or EU-RoActemra administered as IV infusion every 4 weeks (Q4W) in combination with Methotrexate (MTX) (between 10 to 25 mg/week given orally, parenterally, IM or SC) and folic acid (≥5 mg/week orally) in patients with moderate to severe RA. The PK was evaluated as secondary objective with the endpoint of serum tocilizumab concentration (C_{trough}) at each time point up to Week 52.

PK results: Serum concentrations of tocilizumab in the Treatment period I and the Treatment period II subset are summarised by treatment group in **Table 13** and **Table 14** respectively.

The serum concentrations were generally similar between the CT-P47 and RoActemra groups in the PK analysis set during the Treatment period I. The observed tocilizumab C_{trough} concentrations (mean ± SD) on Week 20 were 14.8 µg/ml ± 11.2 µg/ml for CT-P47 and 15.7 µg/ml ± 11.3 µg/ml for RoActemra being in line with the concentrations previously reported for the reference product. In Treatment Period II (Week 24 to Week 52/EOS), switching RoActemra treatment to CT-P47 did not have significant effect on the tocilizumab concentrations as the C_{trough} were generally comparable between CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups up to Week 52 (EOS) treatment. On week 40, the group of patients switched to CT-P47 showed slightly higher mean C_{trough} than the other two groups, presumably because of higher concentrations for some patients on that time point. However, the median serum concentrations were similar among the groups (14400.00 ng/mL, 13500.00 ng/mL, and 14450.00 ng/mL in the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups, respectively).

Table 13 Descriptive statistics of tocilizumab serum concentrations (ng/ml) for PK analysis set / Treatment period I.

Visit Statistics	CT-P47 (N=234)	RoActemra (N=237)
Week 0		
n[(a)]	231	233
Mean ± SD	374.11 ± 5554.125	454.94 ± 6944.291
Median (Minimum, Maximum)	0.00 (0, 84400)	0.00 (0, 106000)
CV%	1484.61	1526.43
Geometric Mean	N.C.	N.C.
Week 4		
n	227	213
Mean ± SD	7769.13 ± 13308.485	7408.45 ± 17319.472
Median (Minimum, Maximum)	6280.00 (98.8, 191000)	5500.00 (82.7, 191000)
CV%	171.30	233.78
Geometric Mean	4545.02	3787.91
Week 8		
n	221	210
Mean ± SD	13597.90 ± 20196.236	12678.85 ± 22622.064
Median (Minimum, Maximum)	9700.00 (114, 220000)	9585.00 (116, 263000)
CV%	148.52	178.42
Geometric Mean	8505.13	7315.57
Week 12		
n	205	208

Visit Statistics	CT-P47 (N=234)	RoActemra (N=237)
Mean ± SD	14946.07 ± 10454.412	14038.48 ± 11325.349
Median (Minimum, Maximum)	12500.00 (90.8, 61800)	11700.00 (102, 71600)
CV%	69.95	80.67
Geometric Mean	11186.90	9271.79
Week 16		
n	204	202
Mean ± SD	15616.83 ± 15680.419	16019.18 ± 15026.117
Median (Minimum, Maximum)	12400.00 (90.2, 162000)	14100.00 (97.8, 164000)
CV%	100.41	93.80
Geometric Mean	9861.67	10262.27
Week 20		
n	197	193
Mean ± SD	14834.57 ± 11177.373	15677.34 ± 11250.953
Median (Minimum, Maximum)	13600.00 (83.4, 59700)	14500.00 (152, 61300)
CV%	75.35	71.77
Geometric Mean	8692.62	9925.00
Week 24		
n	194	197
Mean ± SD	14627.73 ± 11142.571	15142.74 ± 11626.578
Median (Minimum, Maximum)	12250.00 (81.9, 54700)	13400.00 (97.5, 58100)
CV%	76.17	76.78
Geometric Mean	8934.56	9480.61

[a)] A total of 7 patients (3 patients in the CT-P47 and 4 patients in the RoActemra) did not perform pharmacokinetic tests at baseline due to site mistaken.

Table 14 Descriptive statistics of tocilizumab serum concentrations (ng/ml) for PK-Treatment period II subset

Visit	CT-P47 Maintenance (N=207)		RoActemra Maintenance (N=97)		Switched to CT-P47 (N=100)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Week 24	185	14851.3 (11063.48)	89	13812.1 (10634.83)	91	16630.1 (11963.72)
Week 28	178	16774.2 (15252.26)	84	15474.8 (11823.35)	88	18070.8 (14017.53)
Week 32	178	17642.8 (14980.12)	87	17139.3 (12929.94)	90	19818.0 (19291.69)
Week 36	180	14621.7 (13415.55)	86	17424.4 (18610.61)	91	17319.4 (14643.96)
Week 40	182	17977.5 (17195.75)	81	16773.8 (13844.35)	84	22396.8 (21165.79)
Week 44	177	17225.3 (19577.34)	84	17207.3 (16010.52)	89	18493.4 (17066.33)
Week 48	176	17031.4 (17208.47)	83	18706.4 (22483.75)	91	17131.8 (13453.57)
Week 52 (EOS)	178	16731.4 (12991.47)	82	17406.2 (12921.93)	88	17316.2 (13874.57)

Special populations

The PK studies included healthy volunteers of 18 to 55 years of age. The number of elderly patents in the phase 3 study CT-P47 3.1 are given in the **Table 15**.

Table 15 Age ranges studied in the elderly population in phase 3 study CT-P47 3.1

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
CT-P47 EU-RoActemra	54 / 234 (23.1%) 52 / 237 (21.9%)	0	0

Pharmacokinetic interaction studies

Drug-drug-interaction studies have not been conducted, and they are not required.

2.6.2.2. Pharmacodynamics

Mechanism of action

Tocilizumab is an IL-6-Receptor (R) monoclonal antibody (mAb) of the immunoglobulin (Ig)G1κ subclass directed against both the membrane-bound IL-6R (mIL-6R) and the soluble IL-6R (sIL-6R). Tocilizumab binds specifically to both mIL-6R and sIL-6R and has been shown to inhibit IL-6-mediated signalling through these receptors. The tocilizumab/receptor complex cannot be bioactive since it is unable to affect the dimerisation of the gp130 molecule. In the absence of this dimerisation, the IL-6 signal is completely blocked. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis (RA).

Primary and secondary pharmacology

PD in clinical trials

No PD assessment was carried out in the Phase 1 studies (CT-P47 1.1; CT-P47 1.2; CT-P47 1.3) and Phase 3 study CT-P47 3.2. In study CT-P47 3.1, conducted in patients with moderate to severe rheumatoid arthritis, the calculation of DAS28, the primary efficacy endpoint, was carried out by both the collected value of erythrocyte sedimentation rate (ESR) and level of C-reactive protein (CRP). It should be noted that ESR and CRP are unspecific and affected by concomitant infections and other concomitant diseases in addition to impact by tocilizumab and as such not very strong measures on PD of tocilizumab. Concentrations of ESR and CRP were not included in the study as PD or efficacy endpoints. Results on DAS28 and other efficacy endpoints are assessed in *Section 2.6.5 Clinical Efficacy* of this AR. Absolute neutrophil count (ANC) and sIL-6R were collected at baseline and thereafter at every scheduled visit as part of clinical laboratory tests but not as predefined endpoints.

Descriptive statistics for actual result and change from baseline of sIL-R6 are given in **Table 16**. The mean change from baseline of sIL-6R during the Treatment Periods I and II was similar among the groups in the Safety set and Safety – Treatment Period II subset.

Table 16 Mean (SD) for actual value and change from baseline of soluble interleukin-6 receptor (sIL-6R) (ng/mL): Safety set and safety - treatment period II subset, study CT-P47 3.1

Visit Statistic	CT-P47 (N=234)	RoActemra (N=237)	
	Change From Baseline		
Baseline [a]			
n	234	237	
Mean (SD)	32.92 (10.259)	33.18 (12.010)	
Week 4 [b]			
n	230	230	
Mean (SD)	376.11 (124.126)	346.16 (144.082)	
Week 8 [b]			
n	226	224	
Mean (SD)	536.71 (268.755)	460.13 (223.408)	
Week 12 [b]			
n	220	225	
Mean (SD)	517.23 (288.616)	508.48 (265.137)	
Week 16 [b]			
n	221	224	
Mean (SD)	518.00 (262.385)	494.09 (289.082)	
Week 20 [b]			
n	220	225	
Mean (SD)	549.60 (351.524)	565.02 (362.079)	
Week 24 [b]			
n	220	224	
Mean (SD)	435.80 (244.284)	445.52 (260.449)	
Visit **Statistic**	**CT-P47 Maintenance** **(N=225)**	**RoActemra** **Maintenance (N=109)**	**Switched to CT-P47** **(N=110)**
Week 24 [b]			
n	219	108	108
Mean (SD)	437.73 (243.142)	440.53 (263.203)	469.46 (252.013)
Week 28 [b]			
n	214	103	102
Mean (SD)	446.07 (288.850)	422.86 (273.849)	456.31 (268.035)
Week 32 [b]			
n	220	105	106
Mean (SD)	329.39 (181.846)	342.47 (171.075)	354.27 (205.942)
Week 36 [b]			
n	219	104	104
Mean (SD)	311.73 (173.730)	319.63 (180.670)	337.11 (176.739)
Week 40 [b]			
n	218	100	99
Mean (SD)	342.19 (181.696)	330.59 (174.856)	355.71 (174.905)
Week 44 [b]			
n	214	101	106
Mean (SD)	325.11 (187.928)	333.52 (186.421)	378.59 (236.650)
Week 48 [b]			
n	216	102	104
Mean (SD)	314.80 (223.388)	346.04 (230.380)	354.93 (221.890)
Week 52 (EOS) [b]			
n	219	104	104
Mean (SD)	499.78 (345.780)	450.80 (314.470)	486.68 (339.073)

Abbreviations: EOS, end of study; SD, standard deviation.
[a] For the baseline value, actual results were presented.
[b] For values other than baseline, change from baseline results were presented.

From Week 24, the mean change from baseline of sIL-6R showed decreasing trend which might be attributed to the dose modification. As the study was proceeded, the number of patients with dose skip, or dose reduction according to the protocol criteria was getting increased until mid or late of the study period, and the number of patients with study drug discontinuation without study termination were getting increased until the end of the study (data not shown for brevity).

The increase of mean change from baseline at Week 52 (EOS) attributed by some patients with high level of sIL-6R at EOS visit only, but this did not affect the overall efficacy results. In addition, the mean changes from baseline were similar among the treatment groups.

Immunological events

Frequencies of ADAs and NAbs

Frequencies of ADAs and NAbs for the healthy volunteer studies are displayed in in **Table 17**. (Study CT-P47 1.1 Part 2), **Table 18** (Study CT-P47 1.2) and **Table 19** (Study CT-P47 1.3).

Table 17 Frequency of positive ADA/NAb in study CT-P47 1.1 part 2 (safety set)

Visit ADA Result NAb Result	CT-P47 (N=144) n (%)	EU-RoActemra (N=140)
Day 1 (Pre-dose)		
ADA Positive	1 (0.7)	1 (0.7)
NAb Positive	0	0
Day 13		
ADA Positive	0	4 (2.9)
NAb Positive	0	1 (0.7)
Day 43 (EOS)		
ADA Positive	20 (13.9)	28 (20.0)
NAb Positive	17 (11.8)	19 (13.6)
Post-treatment positive (Up to Day 43)		
ADA Positive	20 (13.9)	29 (20.7)
NAb Positive	17 (11.8)	20 (14.3)

Abbreviations: ADA, anti-drug antibody; EOS, end-of-study; EU, European Union; n, number of subjects; NAb, neutralizing antibody.
Note: The NAb assessments were only made on samples with an ADA result of 'Positive'.

Table 18 Frequency of positive ADA/NAb in study CT-P47 1.2 (safety set)

Visit ADA Result NAb Result	CT-P47 (N=45)	EU-RoActemra (N=43)	US-Actemra (N=44)
	n (%)		
Day 1 (Pre-dose)			
ADA Positive	2 (4.4)	1 (2.3)	0
NAb Positive	0	0	0
Day 15			
ADA Positive	1 (2.2)	0	0
NAb Positive	0	0	0
Day 56 (EOS)			
ADA Positive	4 (8.9)	1 (2.3)	2 (4.5)
NAb Positive	2 (4.4)	0	1 (2.3)
Post-treatment (Up to Day 56)			
ADA Positive	5 (11.1)	1 (2.3)	2 (4.5)
NAb Positive	2 (4.4)	0	1 (2.3)

Abbreviations: ADA, anti-drug antibody; EOS, end-of-study; EU, European Union; n, number of subjects; NAb, neutralizing antibody; US, United States.
Note: The NAb assessments were only made on samples with an ADA result of 'Positive'.

Table 19 Frequency of positive ADA/NAb in study CT-P47 1.3 (safety set)

Visit ADA Result NAb Result	CT-P47 AI (N=153)	CT-P47 PFS (N=157)
	n (%)	
Day 1 (Pre-dose)		
ADA Positive	3 (2.0)	0
NAb Positive	0	0
Day 13		
ADA Positive	0	0
NAb Positive	0	0
Day 43 (EOS)		
ADA Positive	26 (17.0)	32 (20.4)
NAb Positive	12 (7.8)	14 (8.9)
Post-treatment (Up to Day 43)		
ADA Positive	26 (17.0)	32 (20.4)
NAb Positive	12 (7.8)	14 (8.9)

Abbreviations: ADA, anti-drug antibody; AI, auto-injector; EOS, end-of-study; n: number of subjects; NAb, neutralizing antibody; PFS, pre-filled syringe.

Studies in RA patients

In study CT-P47 3.1, conducted in RA patients and with IV administered tocilizumab, 19 (4.0%) patients reported positive ADA, and all patients showed negative NAb at Week 0. The number (%) of patients who had positive ADA results at end of Treatment Period (TP) I (Week 24) was 6 (2.6%) patients in the CT-P47 group and 5 (2.1%) patients in the RoActemra group. Of the patients with positive ADA results at Week 24, 3 (1.3%) patients each in the CT-P47 and RoActemra groups were also positive for NAb results. At Week 52 (EOS), there were 2/225, 0/109 and 3/110 ADA positive

subjects in the CT-P47 Maintenance, RoActemra Maintenance and Switched to CT-P47 groups, respectively. All of the ADA positive subjects at Week 52 were NAb negative. (**Table 20**).

Table 20 Summary of immunogenicity results (overall period): safety set

Visit	CT-P47 (N=234)	RoActemra (N=237)	
ADA Result	**Number (%) of patients**		
NAb Result			
Week 0 [a]			
Positive	8 (3.4)	11 (4.6)	
Positive	0	0	
Negative	8 (3.4)	11 (4.6)	
Negative	223 (95.3)	222 (93.7)	
Week 24			
Positive	6 (2.6)	5 (2.1)	
Positive	3 (1.3)	3 (1.3)	
Negative	3 (1.3)	2 (0.8)	
Negative	214 (91.5)	217 (91.6)	
Visit	**CT-P47 Maintenance (N=225)**	**RoActemra Maintenance (N=109)**	**Switched to CT-P47 (N=110)**
ADA Result	**Number (%) of patients**		
NAb Result			
Week 24			
Positive	6 (2.7)	1 (0.9)	4 (3.6)
Positive	3 (1.3)	1 (0.9)	2 (1.8)
Negative	3 (1.3)	0	2 (1.8)
Negative	214 (95.1)	107 (98.2)	104 (94.5)
Week 52 (EOS)			
Positive	2 (0.9)	0	3 (2.7)
Positive	0	0	0
Negative	2 (0.9)	0	3 (2.7)
Negative	208 (92.4)	102 (93.6)	99 (90)

Abbreviations: ADA, antidrug antibody; EOS, end of study; NAb, neutralizing antibody.

Note: The ADA test involved both screening and confirmatory assays to confirm true positive results. Samples that were potentially positive in the screening assay were spiked with excess study drug to determine if patients were a true positive, labelled 'Positive'. The NAb screening assessments were only made on samples with an ADA confirmatory assay result of 'Positive'.

[a] A total of 7 patients (3 patients in the CT-P47 and 4 patients in the RoActemra) did not perform immunogenicity tests at baseline due to site mistaken.

Of the patients who had no ADA-positive result before the first study drug administration in Treatment Period II and who had at least 1 ADA results in Treatment Period II, 6/412 (1.5%) patients had positive conversion in ADA (2/209 [1.0%] patient for the CT-P47 maintenance group, 4/100 [4%] patients for the RoActemra maintenance group, and none for the switched to CT-P47 group). Of the patients who did not have any NAb positive result before the first study drug administration in

Treatment Period II and had at least 1 ADA results in Treatment Period II, 3/423 (0.7%) patients had positive conversion in NAb (2/213 [0.9%] for the CT-P47 maintenance group, 1/105 [1.0%] for the RoActemra maintenance group, and none for the switched to CT-P47 group (**Table 21**).

Table 21 Summary of positive conversion in ADA or NAb (treatment period I: safety set and treatment period II: safety-treatment period II subset)

	CT-P47 (N=234)	RoActemra (N=237)	
Treatment Period I			
Positive Conversion in ADA	6/223 (2.7)	4/222 (1.8)	
Positive Conversion in NAb	10/231 (4.3)	8/233 (3.4)	
	CT-P47 Maintenance (N=225)	**RoActemra Maintenance (N=109)**	**Switched to CT-P47 (N=110)**
Treatment Period II			
Positive Conversion in ADA	2/209 (1.0%)	4/100 (4%)	0/103
Positive Conversion in NAb	2/213 (0.9%)	1/105 (1.0%)	0/105

Abbreviations: ADA, antidrug antibody; EOS, end-of-study; NAb, neutralizing antibody.
Note: For Treatment Period I, the numerator was 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 Period II. The denominator was the number of patients who had at least one ADA result after first study drug administration in Treatment Period I and before the first study drug administration in Treatment Period II and had not any ADA positive (in case of ADA summary) or NAb positive (in case of NAb summary) result before the first study drug administration. For Treatment Period II, the numerator was the number of patients with at least one ADA or NAb positive result after first study drug administration in Treatment Period II. The denominator was the number of patients who had at least one ADA result after first study drug administration in Treatment Period II, and had not any ADA positive (in case of ADA summary) or NAb positive (in case of NAb summary) result before the first study drug administration in Treatment Period II.

Table 22 presents the immunogenicity results for Study CT-P47 3.2 in RA patients and SC administered tocilizumab.

Table 22 Frequency of positive ADA/NAb in study CT-P47 3.2 (safety set)

Visit ADA Result NAb Result	CT-P47 SC (N=33) n (%)
Week 0 (Pre-dose)	
ADA Positive	1 (3.0)
NAb Positive	0
Week 2 (Pre-dose)	
ADA Positive	1 (3.0)
NAb Positive	0
Week 4 (Pre-dose)	
ADA Positive	1 (3.0)
NAb Positive	1 (3.0)
Week 8 (Pre-dose)	
ADA Positive	0
NAb Positive	0
Week 12 (EOS)	
ADA Positive	1 (3.0)
NAb Positive	1 (3.0)
Post-treatment (Up to Week 12)	
ADA Positive	2 (6.1)
NAb Positive	2 (6.1)

Abbreviations: ADA, anti-drug antibody; EOS, end-of-study; n: number of subjects; NAb, neutralizing antibody; SC, subcutaneous.

Impact of ADA on PK

The immunogenicity of CT-P47 and reference drug, in terms of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs), was assessed at baseline and post treatment. The sampling time points for immunogenicity in each clinical study of CT-P47 are given in **Table 23**.

The ADA negative subset of subjects in PK set had only "Negative" result in immunogenicity ADA test after receiving a single dose of study drug. The subjects in the PK set who showed at least one "Positive" result in ADA test after receiving a single dose of study drug was considered as ADA positive subset.

Table 23 Immunogenicity sampling time points in clinical studies of CT-P47

Clinical study	Sampling time point
Study CT-P47 1.1[1]	Days 1, 13 and 43 (EOS)
Study CT-P47 1.2[1]	Days 1, 15 and 56 (EOS)
Study CT-P47 1.3[1]	Days 1, 13 and 43 (EOS)
Study CT-P47 3.1[2]	Weeks 0, 4, 8, 12, 16, 24, 32, 40, 48 and 52 (EOS)
Study CT-P47 3.2[2]	Weeks 0, 2, 4, 8 and 12 (EOS)

EOS: End-of-Study

[1] Samples for immunogenicity analysis on Day 1 were obtained prior to the study drug administration.

Clinical study	Sampling time point

[2] Samples for immunogenicity analysis at all time points were obtained prior to the study drug administration except for EOS.

Study CT-P47 1.1 - Subcutaneous administration to healthy volunteers

In the Part 2 of the study, 20 [13.9%] and 29 [20.7%] subjects in the CT-P47 and EU-RoActemra groups, respectively, had at least one ADA-positive result after treatment. In total 17 (11.8%) and 20 (14.3%) subjects showed NAb positive result, respectively. The primary PK parameters for the ADA negative and ADA-positive subgroups by treatment arm are presented in **Table 24**. Overall, the primary PK parameters, C_{max}, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}last}$, tended to be slightly lower in the ADA-positive subjects compared to ADA-negative subjects in both treatment arms.

Table 24 Primary pharmacokinetic parameters of tocilizumab by treatment group and ADA status following subcutaneous administration (post-treatment ADA status regardless of pre-dose result) in study CT-P47 1.1 Part 2 (PK set)

Parameter Statistic	CT-P47 (N=144)		EU-RoActemra (N=140)	
	ADA Negative	ADA Positive	ADA Negative	ADA Positive
C_{max} (µg/mL)				
n	124	20	111	29
Mean	10.46	9.535	9.954	9.346
Median	10.30	9.300	9.600	9.390
Min	0.892	2.77	1.77	3.07
Max	22.9	17.5	19.9	16.1
$AUC_{0\text{-}inf}$ (day*µg/mL)				
n	119	19	107	29
Mean	95.700	85.849	87.013	82.186
Median	92.710	79.086	80.360	83.664
Min	4.67	18.56	11.03	21.39
Max	216.24	193.15	235.92	144.90
$AUC_{0\text{-}last}$ (day*µg/mL)				
n	124	20	110	29
Mean	94.073	83.239	85.085	81.124
Median	90.170	77.198	76.394	79.708
Min	4.33	18.15	10.81	20.81
Max	215.72	175.29	235.71	144.46

Study CT-P47 1.2 – Intravenous infusion to healthy volunteers

The number of ADA positive subjects after intravenous administration of tocilizumab was low in the three treatment groups. Five subjects in CT-P47 group, one subject in EU-RoActemra group and 2 subjects in US-Actemra group were tested as ADA positive during the study. The primary PK parameters for the ADA negative and ADA-positive subgroups by treatment arm following intravenous infusion of CT-P47, EU-RoActemra and US-Actemra are presented in **Table 25**. Overall, the primary PK

parameters, C_{max}, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}last}$, tended to be slightly lower in the ADA-positive subjects compared to ADA-negative subjects in both treatment arms.

Table 25 Primary pharmacokinetic parameters of tocilizumab by treatment group and ADA status (post-treatment ADA status regardless of pre-dose result) following intravenous infusion in study CT-P47 1.2 (PK set)

Parameter Statistic	CT-P47 (N=45)		EU-RoActemra (N=43)		US-Actemra (N=44)	
	ADA Negative	ADA Positive	ADA Negative	ADA Positive	ADA Negative	ADA Positive
C_{max} (µg/mL)						
n	40	5	42	1	42	2
Mean	157.8	144.2	159.1	141.0	161.7	145.5
Median	156.5	147.0	161.5	141.0	158.0	145.5
Min	121	126	118	141	114	126
Max	200	158	197	141	196	165
$AUC_{0\text{-}inf}$ (hour*µg/mL)						
n	40	5	41	1	42	2
Mean	27318.700	25814.955	27781.346	26918.796	29233.858	27536.487
Median	27647.894	25235.190	27505.055	26918.796	28534.870	27536.487
Min	19524.42	23445.60	21536.31	26918.80	20250.44	24999.22
Max	36593.39	28276.64	36712.55	26918.80	37525.54	30073.75
$AUC_{0\text{-}last}$ (hour*µg/mL)						
n	40	5	42	1	42	2
Mean	27213.501	25779.153	27782.603	26382.760	29009.144	27277.382
Median	27555.979	25216.267	27459.583	26382.760	28469.641	27277.382
Min	19507.53	23395.72	21514.97	26382.76	20236.61	24513.37
Max	36549.57	28251.43	36685.53	26382.76	37476.10	30041.40

Study CT-P47 1.3 – Subcutaneous administration via AI and PFS in healthy volunteers

Following SC administration CT-P47, 26 / 153 subjects (17.0%) were ADA positive in the AI treatment arm and 32 / 157 (20.4%) were ADA positive in the PFS treatment arm. At EOS visit, 26 (8.4%) subjects had NAb positive results with 12 (7.8%) and 14 (8.9%) subjects in the CT-P47 AI and CT-P47 PFS treatment groups, respectively. The ADA positive subgroups of subjects showed slightly lower serum tocilizumab concentrations compared to ADA negative subgroup and consequently slightly lower primary PK parameters (**Table 26**). However, no apparent differences in secondary PK parameters were observed.

Table 26 Primary PK parameters of tocilizumab by treatment group and ADA status

PK Parameter (unit) Statistics	ADA Negative Subset (N=252)		ADA Positive Subset (N=58)	
	CT-P47 AI (N=127)	CT-P47 PFS (N=125)	CT-P47 AI (N=26)	CT-P47 PFS (N=32)
$AUC_{0\text{-}inf}$ (day·µg/mL)[a]				
n	117	120	23	32
Mean (SD)	90.632 (44.2527)	94.766 (44.1189)	87.392 (39.0094)	89.344 (38.1636)
CV%	48.8267	46.5554	44.6374	42.7152
Geometric mean	80.139	83.468	78.406	82.306
Median	82.943	92.491	80.772	79.859
Minimum, Maximum	16.43, 255.11	12.02, 215.38	35.60, 153.73	36.89, 194.70
C_{max} (µg/mL)[b]				
n	124	125	26	32
Mean (SD)	9.817 (4.4947)	10.81 (4.2742)	9.848 (3.8297)	10.32 (4.7433)
CV%	45.784	39.556	38.888	45.977
Geometric mean	8.795	9.794	9.093	9.489
Median	9.435	11.10	9.505	9.415
Minimum, Maximum	2.19, 29.5	1.56, 23.4	4.76, 15.5	4.76, 27.6

(a) 12 subjects (9 subjects in the CT-P47 AI group and 3 subjects in the CT-P47 PFS group) who had an adjusted coefficient of determination (adjusted R^2) of <0.85 were excluded from the $AUC_{0\text{-}inf}$ analysis. Four subjects and 2 subjects in the CT-P47 AI and PFS groups, respectively, did not have at least 3 timepoints after C_{max} and thus, $AUC_{0\text{-}inf}$ analysis was not available.
(b) There were 3 subjects in AI group who had their last observed concentration as the highest value; all were early withdrawal before Day 4. Since truncated profiles of these subjects may not represent real PK profiles, all parameters (C_{max}, T_{max}, and $AUC_{0\text{-}last}$) derived from these subjects were considered not reliable and excluded from the analysis.

Study CT-P47 3.1 – Intravenous infusion to RA patients

Results for serum concentrations of tocilizumab by ADA status are only available for Treatment Period I (TP I) up to Week 24 of the study. The final CSR for CT-P47 3.1 does not include the information of the drug concentrations by ADA status. However, the number (%) of patients who had positive ADA results at Week 52 (EOS) was low: 2 (0.9%) and 3 (2.7%) in the CT-P47 maintenance and the switched to CT-P47 group, respectively, and none in the RoActemra maintenance group (**Table 27**). Of the patients with positive ADA results at Week 52 (EOS), none was positive for NAb results.

In both treatment arms, CT-P47 and EU-RoActemra, the ADA positive subgroup of RA patients showed lower serum trough concentrations of tocilizumab than ADA negative subgroup during TP I (**Table 27**). The serum concentrations and the extent of change between the ADA positive to ADA negative subgroup were comparable between the two treatment arms. Since no concern arises from the results of TP I that immunogenicity would have a different impact on drug exposure with CT-P47 vs. RoActemra and since ADA positivity was low during TP II, the results of tocilizumab concentrations by ADA status for TP II were not requested.

Table 27 Serum concentrations (C_{trough}) of tocilizumab (µg/ml) by ADA status in study CT-P47 3.1. (treatment period I): PK set

Visit	CT-P47 (N=222)				EU-RoActemra (N=224)			
	ADA positive		ADA negative		ADA positive		ADA negative	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Week 4	11	3367.09 (3602.545)	216	7993.30 (13584.254)	12	2841.14 (2250.393)	201	7681.12 (17786.430)
Week 8	11	7549.09 (5426.254)	210	13914.75 (20637.838)	11	5860.45 (4889.364)	199	13055.75 (23157.198)
Week 12	10	9603.00 (3781.399)	195	15220.07 (10616.878)	10	8488.90 (7575.128)	198	14318.76 (11424.121)

Visit	CT-P47 (N=222)				EU-RoActemra (N=224)			
	ADA positive		ADA negative		ADA positive		ADA negative	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Week 16	12	6701.42 (5298.079)	192	16174.05 (15949.945)	9	12276.67 (7106.038)	193	16193.70 (15283.216)
Week 20	10	9312.00 (5344.166)	187	15129.89 (11337.601)	8	9911.00 (7836.686)	185	15926.70 (11324.443)
Week 24	9	9363.89 (6013.480)	185	14883.81 (11279.907)	8	7887.88 (5634.762)	189	15449.83 (11722.322)

Note: Concentrations below the lower limit of quantification (BLQ) prior to the first administration (Week 0) are set to zero. All other BLQ values are treated as missing. Samples were collected at pre-dose (prior to the beginning of study drug administration). ADA negative subgroup was defined as patients who showed only negative ADA results after first study drug administration in Treatment Period I (up to Week 24). ADA positive subgroup was defined as patients who showed at least one positive ADA result after first study drug administration in Treatment Period I (up to Week 24).

Impact of ADA on efficacy

The impact of ADA on efficacy was assessed in Study CT-P47 3.1. Results of the primary efficacy endpoint (the mean change from baseline of Disease Activity Score using 28 joint counts [DAS28 (ESR)] score at Week 12) by ADA status at Week 12 was summarised in **Table 28** for the intent-to-treat (ITT) Set. According to the applicant, due to the small sample size of ADA positive subgroups, it is difficult to derive any conclusion regarding the correlation between ADA positivity and the efficacy.

Table 28 Summary of change from baseline of DAS28 (ESR) score at Week 12 by ADA status at week 12 in study CT-P47 3.1 (ITT set)

Statistic	CT-P47		EU-RoActemra	
	ADA positive at Week 12	ADA negative at Week 12	ADA positive at Week 12	ADA negative at Week 12
n	6	213	4	220
Mean	-3.003	-3.099	-1.816	-3.099
SD	1.7474	1.3002	1.6781	1.3211
Minimum	-5.23	-6.15	-4.26	-6.15
Median	-3.507	-3.123	-1.229	-3.165
Maximum	-0.65	1.19	-0.54	-0.13

Note: If any individual component was missing, the DAS28 score was not calculated.
Abbreviation: ADA, anti-drug antibody; DAS28, disease activity score using 28 joint counts; EU, European Union; n, number of patients; SD, standard deviation

The applicant intended to conduct a post-hoc analysis for change from baseline of DAS28 (ESR) score by ADA titre at Week 12, too, in order to find the impact of ADA titre on efficacy, but it was not conducted since there was only one patient with high ADA titre (≥780) value in both treatment groups at Week 12 in the Study CT-P47 3.1.

The impact of NAb on efficacy by NAb status at Week 12 is presented in **Table 29** and the NAb negative subgroup also included the patients who reported ADA negative at Week 12. Due to the small sample size of NAb positive subgroups, the applicant considered it difficult to derive any conclusion regarding the correlation between NAb positivity and the efficacy.

Similar analyses on impact of ADA and NAb on efficacy that were performed for Treatment Period I are not available for the entire duration of the study. However, taking in account the low incidence of ADA, results for the latter part of the study were not requested as no relevant conclusions could be drawn.

Table 29 Summary of change from baseline of DAS28 (ESR) score at week 12 by NAb status at week 12 in study CT-P47 3.1 (ITT set)

Statistic	CT-P47		EU-RoActemra	
	NAb positive at Week 12	NAb or ADA negative at Week 12	NAb positive at Week 12	NAb or ADA negative at Week 12
n	4	215	3	221
Mean	-3.036	-3.098	-1.000	-3.105
SD	1.2624	1.3129	0.4812	1.3204
Minimum	-3.96	-6.15	-1.50	-6.15
Median	-3.507	-3.123	-0.957	-3.170
Maximum	-1.17	1.19	-0.54	-0.13

Note: If any individual component was missing, the DAS28 score was not calculated.
Abbreviation: EU, European Union; NAb, neutralizing antibody; DAS28, disease activity score using 28 joint counts; SD, standard deviation

Impact of ADA on safety

The impact of ADA on safety was assessed in Study CT-P47 3.1. These results were submitted with the MAA up to Week 32. No similar analysis has been included for the entire study duration (up to Week 52) in the final CSR of study CT-P47 3.1.

The proportion of patients who experienced any TEAE, treatment-emergent serious adverse event (TESAE), and TEAE classified as a hypersensitivity reaction were analysed up to Week 32 by post-treatment ADA status (**Table 30**). According to the applicant, there was no apparent correlation between the presence of ADA and the occurrence of TEAE, TESAE, or hypersensitivity reactions.

The hypersensitivity reaction in the ADA positive patient in the CT-P47 group was grade 1 rash that resolved without treatment and was considered non-serious.

Three non-serious hypersensitivity reactions were reported in the ADA positive subgroup of EU-RoActemra group. One patient experienced grade 2 rash after study drug administration and recovered with medication. One patient experienced grade 2 pruritus after study drug administration and discontinued study drug. One patient experienced an anaphylactic reaction (grade 2 rash, grade 2 hypotension, and grade 2 electrocardiogram QT prolonged) after study drug administration. The patient discontinued the study drug due to this event. Safety data up to Week 52 are included in the final CSR submitted with the response, but the TEAEs, TESAEs and TEAEs classified as hypersensitivity reaction have not been analysed by ADA status. During TP II (24 to 52 weeks), there was only one patient with at least one TEAE classified as hypersensitivity reaction in the in the CT-P47 group and none in the other study groups; the ADA status of the patient is not reported in the CSR.

Table 30 Proportion of patients with TEAE, TESAE, TEAE classified as hypersensitivity reactions by post-treatment ADA status in study CT-P47 3.1 (safety set)

Number of Patients (%) with at Least 1 Adverse Event	Overall Period (up to Week 32 predose)			
	CT-P47 (N=234)		EU-RoActemra (N=237)	
ADA Status	ADA Positive (N=12)	ADA Negative (N=222)	ADA Positive (N=13)	ADA Negative (N=224)
TEAE	10 (83.3)	192 (86.5)	12 (92.3)	188 (83.9)
TESAE	1 (8.3)	13 (5.9)	0	14 (6.3)
Hypersensitivity Reactions	1 (8.3)	2 (0.9)	3 (23.1)	4 (1.8)

Note: ADA negative subgroup was defined as patients who showed only negative ADA results after first study drug administration in Treatment Period I (up to Week 32). ADA positive subgroup was defined as patients who showed at least one positive ADA result after first study drug administration in Treatment Period I (up to Week 32).
Abbreviation: EU, European Union; N, Number of patients; TEAE, Treatment-Emergent Adverse Event; TESAE, Treatment-Emergent Serious Adverse Event.

The applicant also compiled a summary of safety findings for healthy volunteers with very high (≥6240) ADA titres. No immune-related or other AEs were seen in any of these subjects (

Table *31*).

Table 31 The immunogenicity, PK, and safety results of individual subjects with significantly high ADA titre (≥ 6240) in studies CT-P47 1.1 part 2, CT-P47 1.2 and CT-P47 1.3 (safety set)

Study	Subject Number	Treatment Group	Immunogenicity		PK	Safety	
			Highest ADA Titer (Visit)	NAb Result	Serum Concentration (µg/mL) (Visit)	TEAE by PT Reported after High ADA Titer (CTCAE Grade, Relationship to Study Drug)	Immune-related AE
Study CT-P47 1.1 Part 2		CT-P47	6240 (Day 43)	Positive at Day 43	BLQ* (Day 43)	N/A	N/A
		EU-RoActemra	12480 (Day 43)	Positive at Day 43	BLQ* (Day 43)	N/A	N/A
		EU-RoActemra	24960 (Day 43)	Positive at Day 43	BLQ* (Day 43)	N/A	N/A
Study CT-P47 1.2		CT-P47	6240 (Day 56)	Positive at Day 56	BLQ* (Day 56)	N/A	N/A
Study CT-P47 1.3		CT-P47 PFS	12480 (Day 43)	Positive at Day 43	BLQ* (Day 43)	N/A	N/A
		CT-P47 PFS	24960 (Day 43)	Positive at Day 43	BLQ* (Day 43)	N/A	N/A
		CT-P47 PFS	6240 (Day 43)	Positive at Day 43	BLQ* (Day 43)	N/A	N/A

* BLQ value set to missing
Abbreviations: ADA, anti-drug antibody; AE, adverse event; BLQ, below the limit of quantification; CTCAE, Common Terminology Criteria for Adverse Events; EU, European Union; N/A, not applicable; NAb, neutralizing antibody; PK, pharmacokinetics; PFS, pre-filled syringe; PT, preferred term; TEAE, treatment emergent adverse event

2.6.3. Discussion on clinical pharmacology

CT-P47 has been developed as a subcutaneously administered drug product and an intravenously administered drug product. The proposed dosage, routes of administration, and strengths of CT-P47 are identical to those of the reference product, RoActemra. The clinical development of CT-P47 to support biosimilarity consists of two pivotal PK-studies comparing the SC and IV administration of CT-P47 to the EU-originator RoActemra and one Phase 3 efficacy study with patients with moderate to severe RA. In addition, to support the AI presentation, a PK bioequivalence study in healthy volunteers

has been conducted comparing SC administration with PFS which has been used to demonstrate the PK biosimilarity with the originator product. A single SC dose of 162 mg was selected for subjects in the PK equivalence studies CT-P47 1.1 and CT-P47 1.3, and a single IV dose of 8 mg/kg was selected for subjects in the PK equivalence study CT-P47 1.2. Tocilizumab has nonlinear, dose-dependent pharmacokinetics. In theory, this suggests that kinetic comparisons should be carried out at more than one dose level. However, it was not necessary to apply this general requirement in this case because the exposures after SC and IV formulations are markedly different. Therefore, proven similarity among tocilizumab exposures following different administration modes automatically implies similarity at different dose levels. Overall, the clinical development program is considered sufficient from the clinical pharmacokinetic perspective.

Bioanalytical methods

Validated ligand binding assays were used for the quantitation of tocilizumab and detection of ADA and NAb. The applicant has informed the CHMP that the bioanalytical method is able to analyse the unbound concentration of tocilizumab in human serum, thus, tocilizumab bound to sIL-6R or ADAs in human serum cannot be detected. In the PK-similarity studies with healthy volunteers, the mean C_{max} concentrations following SC and IV administration of CT-P47 and EU-RoActemra were consistent with those reported for RA patients in literature for the originator (Abdallah et al., J Clin. Pharmacol. 2017;57(4):459-468). Moreover, majority of tocilizumab in human is assumed to be as free, unbound to sIL-6R because the molar concentrations of tocilizumab exceed that of sIL-6R (RoActermra EPAR, EMEA/26276/2009).

Overall, the applied methods for immunogenicity testing are state-of-the-art and properly validated as required by the relevant EMA Guidelines.

Pharmacokinetic data analysis

The primary PK analysis assessed the bioequivalence of CT-P47 vs. EU-RoActemra in terms of primary PK parameters, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max}. The statistical analysis of the log-transformed primary PK parameters was based on an analysis of covariance (ANCOVA) model with body weight at Day -1, gender, and study centre as covariates. The source SAS outputs for the primary analysis of studies CT-P47 1.1 Part 2, CT-P47 1.2, and CT-P47 1.3 were provided. The applicant conducted an additional statistical evaluation on centre effect and treatment-by-weight interaction term in the clinical studies. Although centre effect was found to be statistically significant in the studies CT-P47 1.2 and CT-P47 1.3, the additional sensitivity analysis shows that the impact of the centre effect is negligible on the biosimilarity conclusion. An additional ANCOVA including treatment-by-weight term as fixed effect in the primary analysis of the studies convincingly demonstrated that formulation-weight interaction does not exist, hence, the biosimilarity conclusion is valid regardless of weight.

The industry-standard software, WinNonlin, was used to obtain the pharmacokinetic parameters. The WinNonlin outputs were submitted and reviewed for those concentration plots where AUC_{inf} could not be estimated. At the terminal phase, for whatever reason, the elimination accelerates and WinNonlin could not handle these situations. This is not software error but rather that the general industry standard criteria that cannot handle unusual situations, molecules with unusual pharmacokinetics. Nevertheless, the non-evaluable cases are only few percentages of the total sample sizes and do not seem to be definitely formulation specific. Therefore, the bioequivalence conclusions are not affected.

Pharmacokinetics

GCP aspects

The clinical studies were conducted in accordance with the principles of the ICH E6(R2): Good Clinical Practice (GCP). The applicant provided information for inspections of the study sites and/ or CROs by

regulatory agencies following ICH GCP. Furthermore, the applicant carried out an extensive auditing program of the clinical study sites.

Phase 1 PK-equivalence study comparing SC injection (PFS) of CT-P47 and EU-RoActemra (study CT-P47 1.1)

The study was conducted as parallel group design which is appropriate considering the long half-life and immunogenicity of tocilizumab which may compromise the comparison in crossover fashion. The overall study design, blood sample collection schedule and study duration are in line with the scientific advice given by the CHMP. The study was conducted in two Parts which were claimed to be conducted independently. The Part 1 was conducted in one study site (S01) which participated also in the subject recruitment for the Part 2 of the study. However, randomisation of the subjects and the administration of study medications had been completed for Part 1 before the Part 2 began in this study site.

The study drugs were administered subcutaneously in upper arm as fixed dose of 162 mg with PFS which is the currently approved SC dose for the reference product RoActemra. The selected dose and the reference product are acceptable. The batch of EU-RoActemra was purchased from German market.

An interim analysis was made for sample size reassessment as specified in the protocol. The drop-out rate and observed CV% of the primary PK estimates were reviewed by the IDMC. The variance estimation has been extended from the initially planned of 22 days PK-data to up to 43 days as advised by CHMP. Moreover, despite the possibility of type 1 error inflation due to the blinded sample size reassessment, the applicant has evaluated equivalence using nominal 90% confidence intervals rather than adjusting the confidence levels conservatively, as advised by the SAWP. The IDMC did not recommend increasing the sample size and, given the clarity of the results, no further post hoc adjustments to the confidence levels were requested.

In the Part 2, the primary PK endpoints were $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}. According to the CHMP guideline (EMA/CHMP/BMWP/403543/2010), a single dose study after subcutaneous administration should include the $AUC_{0\text{-inf}}$ as the primary parameter and C_{max} as a co-primary parameter. However, there are no objections for inclusion all the three PK parameters as primary endpoints.

Excluded subject data from the $AUC_{0\text{-inf}}$ analysis: In total ten subjects for whom the extrapolated AUC could not be reliably determined (6 in CT-P47 group, 4 in EU-RoActemra group) were excluded from the primary PK analyses for $AUC_{0\text{-inf}}$ as defined in the SAP. The statistical analysis robustly showed equivalence for both AUC parameters ($AUC_{0\text{-inf}}$ and $AUC_{0\text{-last}}$), therefore, the data exclusions are not considered to affect the outcome of the statistical analysis and conclusion of similar pharmacokinetics between test and reference products.

Partial AUCs: The applicant has conducted two Phase I PK-equivalence studies, one with subcutaneous and another with intravenous formulation, thus, partial AUCs to support the extrapolations of the SC data to IV administration are not considered necessary (EMA Clarification on Scientific Advice EMA/SA/000006435, Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-clinical and Clinical Issues EMA/CHMP/BMWP/403543/2010).

When comparing the spaghetti plots of individual serum concentration-time curves between the treatment groups, no clear differences in the patterns were observed between the groups.

The clearance of tocilizumab is concentration-dependent consisting of linear and non-linear clearance. If the reference mAb is eliminated both by target-mediated and non-target mediated mechanisms, comparable PK should be demonstrated where each mechanism of clearance predominates (EMA/CHMP/BMWP/403543/2010). Based on a population PK analysis of tocilizumab in RA patients, nonlinear clearance was dominant component of total clearance at tocilizumab serum concentrations

less than 25 µg/ml (Frey et al. 2010). Thus, as the observed tocilizumab concentrations were below 10 µg/ml (highest individual C_{max} 22.9 µg/ml), non-linear clearance prevails the total clearance following subcutaneous administration. The PK similarity has been compared between the products after intravenous 8 mg/kg as single dose which represents also linear clearance.

ANCOVA analysis indicated similarity of CT-P47 with the EU-RoActemra after subcutaneous administration as the 90% CIs for the geometric mean ratios of the primary PK parameters (AUC_{0-inf}, AUC_{0-last}, C_{max}) were within the equivalence limits of 80.00% and 125.00%. The PK parameters were comparable between the treatment arms.

Phase 1 PK-equivalence study comparing IV infusion of CT-P47, EU-RoActemra and US-Actemra (study CT-P47 1.2)

The study CT-P47 1.2 investigated the PK similarity of the proposed product with the reference product after IV infusion of 8 mg/kg dose which is the highest approved dose of the reference product RoActemra for adult patients in EU. The applicant has justified that the dose provides tocilizumab serum concentrations representing the linear clearance mechanism, thus, demonstrating similarity for linear non-specific clearance mechanisms. This claim is agreed, however at the lower tocilizumab serum concentrations non-linear clearance pathway predominates.

The study design and standardisation are adequate and in line with the scientific advice given by the CHMP. The reference product (EU-RoActemra, US-Actemra) batches were appropriate.

Female subjects were not included in the study. Healthy male subjects are considered as sufficiently homogenous population to detect differences in PK of the treatments.

The statistical analysis of the log-transformed primary PK endpoints was done using an ANCOVA with treatment as fixed effect and with body weight at Day -1 as covariate. The primary analysis model including the baseline covariates was specified in the study protocol as recommended by CHMP scientific advice. Since all the enrolled subjects were male, gender was removed from the covariates in the analysis of covariance model for the primary PK analysis.

Three primary PK estimates, AUC_{0-inf}, AUC_{0-last}, and C_{max}, have been compared by ANCOVA analysis. According to the *Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues* (EMA/CHMP/BMWP/403543/2010), AUC_{0-inf} should be analysed as primary parameter for IV administration. However, there are no objections for testing the three parameters as equivalence was based on acceptability of all of them.

Partial AUCs: The applicant has not provided the analysis of partial AUCs reflecting the linear and non-linear elimination pathways to support the PK similarity of the proposed product as recommended in the CHMP Scientific Advice (EMA/CHMP/SAWP/531258/2020). Based on the population PK analysis by Frey et al. (2010), at concentrations >50 µg/mL, linear CL was the dominant tocilizumab elimination pathway after IV infusion on tocilizumab. At concentrations ~25 µg/mL, both components of total CL contributed equally to the elimination of tocilizumab. Thus, linear CL was predominant up to 168 hours (Day 8) with mean concentrations of 51.06 µg/ml (CV% 14.5%) for CT-P47 and 50.90 µg/ml (CV% 14.3%) for EU-RoActemra and would still have main contribution to total CL up to 336 hours (Day 15) with mean concentrations of 29.21 µg/ml (CV% 16.5%) and 29.83 µg/ml (CV% 15.9%), respectively. As the mean concentrations were highly similar, variation (CV%) were low and the 90% CI for GM ratio were within the equivalence margins 80.00-125.00% for both AUC_{0-t} and AUC_{0-inf}, evaluation of partial AUCs is not considered to provide relevant additional information.

The CT-P47 was confirmed as similar with EU-RoActemra as the 90% CIs for geometric mean ratio of all the three primary PK parameters AUC_{0-inf}, AUC_{0-last}, and C_{max} were within the conventional equivalence margins 85.00% to 125.00%. The secondary parameters (T_{max}, $t_{1/2}$, $\%AUC_{ext}$, λ_z, CL, and

V_z) were comparable between the treatments. Moreover, the study showed PK similarity between CT-P47 and US-Actemra as well as between EU-RoActemra and US-Actemra.

Phase 1 PK study comparing SC administration of CT-P47 with AI to PFS (study CT-P47 1.3)

In a follow up Scientific Advice (EMA/SA/0000087842, 23 June 2022), the CHMP endorsed the applicant's intention to conduct a phase 1 study to compare the PK and safety of CT-P47 auto-injector (AI) and CT-P47 prefilled syringe (PFS) in healthy subjects to establish a bridge to clinical data conducted with the PFS.

The parallel group, single dose study design and blood sampling schedule were similar to the previous SC study comparing the CT-P47 PFS formulation with EU-RoActemra (study CT-P47 1.1). The protein concentration of the batch used for AI presentation was 98.9 % of the labelled claim, but the batches used in the study were acceptable.

The primary PK endpoints were $AUC_{0\text{-}inf}$ and C_{max} as recommended for subcutaneous administration of monoclonal antibodies by the EMA guideline EMA/CHMP/BMWP/403543/2010.

The subcutaneous absorption of tocilizumab following administration using AI was slightly slower compared to PFS as the time to peak concentration was in median 4.0 hours and 3.0 hours for CT-P47 AI and CT-P47 PFS, respectively. Despite this, the geometric mean ratio and 90% CI for both primary PK endpoints, C_{max} and $AUC_{0\text{-}inf}$, were within the equivalence margin of 80.00% to 125.00% indicating bioequivalence of CT-P47 AI and CT-P47 PFS. The secondary PK parameters were comparable between the treatment groups. The additional ANCOVA analysis and calculation of 90% CI for geometric mean T/R ratio of $AUC_{0\text{-}last}$ confirmed the similarity of the extent of exposure between SC CT-P47 administered with AI and PFS as 90% CI was within the equivalence limits of 80.00% to 125.00%.

Pharmacokinetics in patients with moderate to severe RA (study CT-P47 3.1)

CHMP advised to include the common PK endpoints in the multiple-dose setting in the phase 3 study with RA patients to support comparability of the non-specific elimination or use PK modelling (Follow-up Scientific Advice EMA/SA0000050398). However, the applicant did not change the plan and evaluated C_{trough} levels as initially planned. As in the phase 1 PK studies for SC and IV presentations both non-linear and linear elimination pathways were evaluated in healthy volunteers, the descriptive statistics of C_{trough} is considered sufficient to support PK similarity in the selected patient population.

After 8 mg/kg IV infusion Q4W, the steady state is reached for tocilizumab C_{min} within 20 weeks of treatment (RoActemra SmPC). In the study CT-P47 3.1, the observed tocilizumab C_{trough} concentrations (mean ± SD) on Week 20 were 14.8 µg/ml ± 11.2 µg/ml for CT-P47 and 15.7 µg/ml ± 11.3 µg/ml for RoActemra being well in line with the concentrations previously reported for the reference product. In Treatment Period II (Week 24 to Week 52), the C_{trough} remained generally comparable between CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups up to Week 52 (EOS) treatment.

The pivotal phase 1 PK studies were conducted in Asian healthy volunteers in study centres located in South Korea and Japan. The phase 3 study CT-P47 3.1 with RA patients could be considered as bridging study extrapolating PK data obtained in the pivotal phase 1 PK studies with Asian healthy volunteers to the Caucasian patient population. As the proportions of patients with tocilizumab concentrations below limit of quantitation (BLQ) between the groups (test vs. reference) were generally similar and no obvious differences between the treatments were observed, the phase 3 study 3.1 in considered to support similarity of pharmacokinetics between CT-P47 and EU-RoActemra in Caucasian RA patients.

The active substance PK-equivalence study comparing SC injections (PFS) of CT-P47 (Batch 1TFA02) and EU-RoActemra (study CT-P47 1.1) was prepared with interim manufacturing process called process B and not with the final process C. Furthermore, the batch used in the clinical Study CT-P47 3.2 was not manufactured by the commercial process. The lot was produced by drug product (DP) Process SC-2 using Process B drug substance (DS) while the commercial manufacturing process is DP Process SC-3 using Process C DS. This was accepted as no major quality issue has been identified between drug products obtained with process B and C.

Study population in pivotal phase 1 studies

The pivotal phase 1 PK studies (CT-P47 1.1, CT-P47 1.2) as well as the bioequivalence comparing AI vs. PFS (CT-P47 1.3) were conducted in Asian healthy volunteers. Population pharmacokinetic analyses in RA and GCA patients have showed that ethnic origin did not affect the pharmacokinetics of RoActemra. No objections were raised during the consultation period about the PK studies being conducted in a population not representative of the EU population.

Pharmacodynamics

In the Scientific Advice, it was advised (25/03/2021) that an evaluation of e.g. C-reactive protein (CRP) and soluble interleukin-6 receptor (sIL-6R) as secondary endpoints in study CT-P47 3.1, conducted in patients with moderate to severe rheumatoid arthritis, would be valuable to generate further supportive evidence for the conclusion of biosimilarity, which will be based on the totality of evidence. Additionally, the SAWP advised total IL-6 and absolute neutrophil counts (ANC) to be compared as exploratory endpoints. Neither IL-6 or sIL-6R levels are validated PD markers for tocilizumab. It is therefore considered acceptable that circulating IL-6 levels were not measured in the study and that the concentration of sIL-6R was not a predefined endpoint. However, soluble interleukin-6 receptor (sIL-6R) concentrations were collected for assessment of tocilizumab effect in the phase 3 study CT-P47 3.1. There was a similar increase during treatment period I (TP I) in sIL-6R levels in the CT-P47 and RoActemra groups up to Week 24. During treatment period II (TP II) of the study the levels decreased somewhat, obviously due to dose reductions and an increasing number of patients with study drug discontinuation without study termination. The change from baseline (cfb) was similar across the CT-P47 Maintenance, RoActemra Maintenance and Switch to CT-P47 groups in TP II. At Week 52, the cfb of sIl-R6 again increased in all three groups, attributed by some patients with high level of sIL-6R at EOS visit only.

Immunogenicity evaluation

In the phase 3 study, the IV presentations of CT-P47 and RoActemra were compared, including immunogenicity. However, the route of administration can influence the immunogenicity of these therapeutic antibodies. The SC route tends to lead to a slower absorption rate and a longer exposure to the immune system's antigen-presenting cells (APCs) in the skin and subcutaneous tissue. Multiple studies and regulatory experience indicate that the formation of ADAs is generally more frequent with SC administration compared to IV administration. Therefore, from a regulatory perspective, to compare immunogenicity of biosimilar products, a clinical trial with the subcutaneous formulation could be preferred because it may be more sensitive compared to a study in which the IV formulations are compared. However, in light of the closely similar immunogenicity profile of CT-P47 vs. originator, this is not considered crucial.

Immunogenicity results with IV formulation are available for the duration of study CT-P47 3.1, up to 52 weeks, including Treatment Period I (TP I up to 24 weeks) and Treatment Period II (TP II from 24 to 52 weeks). The proportion of patients with positive ADA conversion results were generally similar between groups during TP I (6/223 [2.7%] patients in the CT-P47 group and 4/222 [1.8%] patients in the RoActemra group) and among 3 groups during TP II (2/209 [1.0%] patient for the CT-P47

maintenance group, 4/100 [4%] patients for the RoActemra maintenance group, and none for the switched to CT-P47 group).

Immunogenicity was followed also in Study CT P47 3.2, after SC administration. In this study, 1/33 (3.0%) patient had positive ADA test result at Week 0 (Day 1) prior to study drug administration. This patient did not show positive ADA test results in post-treatment visits until EOS. Two (2/33, 6.1%) patients had positive ADA test results in post-treatment visits until EOS and were also positive for NAb results. No other patients reported positive ADA test results. Overall, CT-P47 AI was well tolerated and the safety profile including immunogenicity of repeat SC administration of CT-P47 was in line with the known safety profile of RoActemra/Actemra. Therefore, results of CT-P47 3.2 mitigates the concern of immunogenicity with SC formulation though only 33 patients participated in Study CT-P47 3.2, and the study lasted only 12 weeks.

The effect of ADA on PK of tocilizumab

Impact of ADA/NAb positivity or titre on tocilizumab concentration was only analysed in study CT-P47 3.1 for TP I of the study. Overall, the ADA positive subgroups showed lower mean AUC and C_{max} values for both CT-P47 and EU-RoActemra treatment compared to ADA negative subgroups following SC and IV administration in healthy volunteers. After intravenous infusion to RA patients, the C_{trough} values were lower in ADA positive subgroup of patients compared to ADA negative patients. The extent of change between the ADA positive to ADA negative subgroup were mainly comparable between the two treatment arms. The number of healthy volunteers and RA patients with at least one ADA positive result after drug administration were comparable in both treatment arms, CT-P47 and EU-RoActemra. The number (%) of patients who had positive ADA results at Week 52 (EOS) was low, and none of the patients with positive ADA results at Week 52 (EOS) was positive for NAb. In light of the low ADA positivity and no concern from the results of TP I that immunogenicity would have a different impact on drug exposure with CT-P47 vs. RoActemra, the results of tocilizumab concentrations by ADA status for TP II were not requested.

The effect of ADA on safety and efficacy of tocilizumab

The development of ADAs did not seem to have any effect on safety during the first 12 weeks of the study. Among healthy volunteers with the highest ADA titres, no AEs were reported. In RA patients in Study CT-P47 3.1, at week 12, the number of ADA positive subjects was 6/219 in the CT-P47 group and 4/224 in the EU-RoActemra group. The number of NAb positive subjects was 4 and 3 in the CT-P47 and EU-Roactemra groups, respectively. Hypersensitivity reactions were overall proportionally more frequent in the ADA-positive subgroup in both treatment groups, but the very small proportion of ADA-positive patients does not allow further conclusions. Similarly, no definite conclusions can be drawn regarding impact of ADA on efficacy based on the few ADA-positive subjects.

Similar analyses on impact of ADA and NAb on efficacy and safety are not available for the entire duration of the study. However, taking in account the low incidence of ADA, results for the latter part of the study are not requested, as no relevant conclusions could be drawn.

2.6.4. Conclusions on clinical pharmacology

The clinical development of CT-P47 to support biosimilarity consists of two pivotal PK-studies comparing the SC and IV administration of CT-P47 to the EU-originator RoActemra in healthy volunteers (Studies CT-P47 1.1, CT-P47 1.2) and one Phase 3 efficacy study with patients with moderate to severe RA (Study CT-P47 3.1). The results support the applicant's claim that there is no clinically meaningful pharmacokinetic (PK) difference between CT-P47 and the reference products (EU-RoActemra and US-Actemra), regardless of the presentation (intravenous or subcutaneous). In

addition, to support the AI presentation, a PK bioequivalence study in healthy volunteers has been conducted comparing SC administration with PFS which has been used to demonstrate the PK biosimilarity with the originator product (Study CT-P47 1.3). Overall, the clinical development program is considered sufficient from the clinical pharmacology perspective. The clinical PK data comparing SC dose of 162 mg as PFS and IV infusion of 8 mg/kg of CT-P47 versus EU-RoActemra supported biosimilarity of the products.

2.6.5. Clinical efficacy

2.6.5.1. Dose response studies

Not applicable for biosimilars.

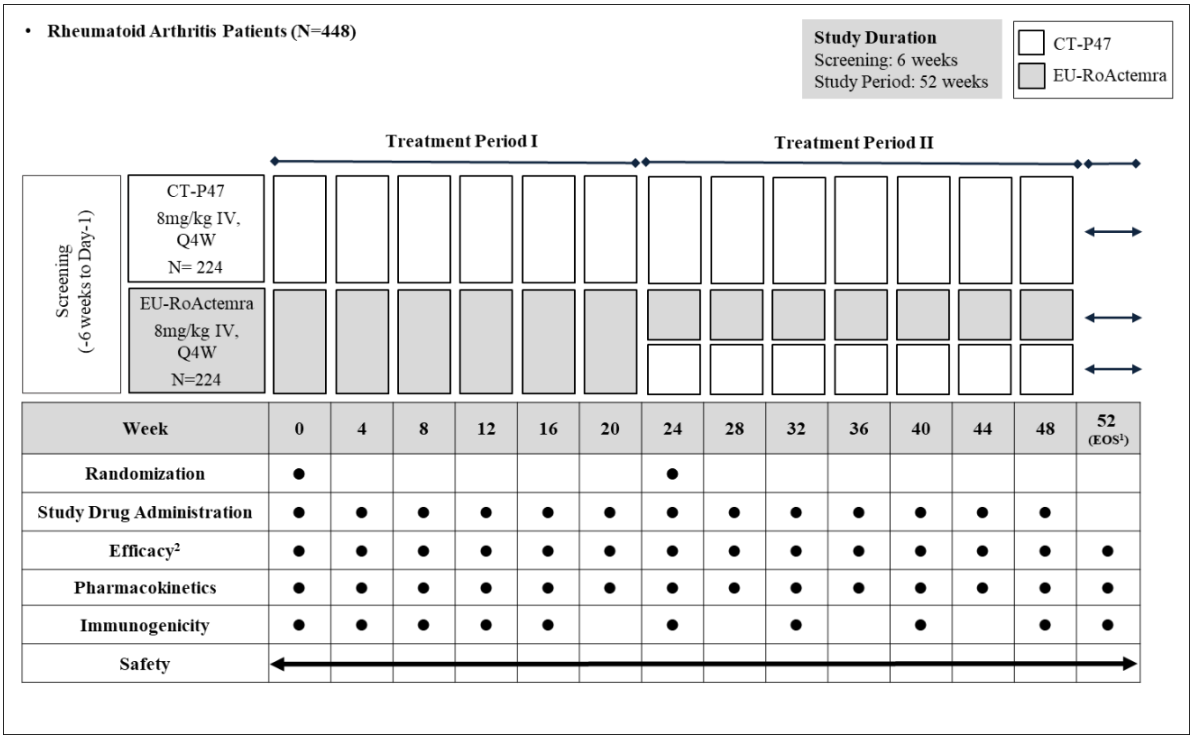
2.6.5.2. Main studies

Study CT-P47 3.1

Methods

Study 3.1 is a randomised double-blind multicentre 52-week clinical trial in patients with rheumatoid arthritis (RA), conducted in 22 study centres in Poland, with principal investigator from Toronto, Canada. The first patient was randomised on 14 Sep 2022 and the last patient's 32-week visit was on 29 Jun 2023. The final CSR (study completion date 23 Nov 2023) was received with the applicant's response to D120 questions.

This study was a randomised, active-controlled, double-blind, multicentre, Phase 3 study designed to evaluate efficacy, PK, and overall safety including immunogenicity of multiple dose (8 mg/kg, not exceeding 800 mg/dose) of either CT-P47 or RoActemra administered by intravenous (IV) every 4 weeks (Q4W) in combination with Methotrexate (MTX) (between 10 to 25 mg/week, oral or parenteral; intramuscular [IM] or subcutaneous(ly) [SC] dose) and folic acid (≥5 mg/week, oral dose). The MTX dose and route were maintained from the beginning to the end of the study.



Abbreviations: EOS, end-of-study; IV, intravenous; Q4W, every 4 weeks.

* Prior to dosing at Week 24, all patients underwent a second randomisation process. Patients who were initially randomised to RoActemra were randomised again in a ratio of 1:1 to either continue with RoActemra or undergo transition to CT-P47. Patients who were randomised to CT-P47 or RoActemra received assigned study drug Q4W from Week 24 and thereafter up to Week 48.
[1] The EOS assessments were performed at Week 52 for all patients who completed or discontinued study drug. The patients who early discontinued from the study drug also visited the study centre until Week 52 by regular scheduled time interval for efficacy and safety assessments, even if they changed their RA medication (including those prohibited by the protocol).
[2] An independent joint count assessor assigned to each study centre assessed joint counts. If possible, it was recommended that the joint count assessments were performed independently by the same person, at each study centre throughout the entire study

Figure 5 Study schema

- **Study Participants**

Main inclusion/exclusion criteria

Female or male patients with moderate to severe active RA, aged 18-75 years, both inclusive, who had a diagnosis of RA according to the 2010 ACR/EULAR classification criteria for at least 24 weeks prior to the first administration of the study drug, were eligible. Patients were required to have moderate to severe disease activity as defined by all the following at screening:

- 6 or more swollen joints (of 66 assessed)
- 6 or more tender joints (of 68 assessed)
- Either an ESR ≥28 mm/hour or a serum CRP concentration ≥1.0 mg/dL (≥10 mg/L)
- DAS28 (ESR or CRP) ≥3.2

Patients were required to have been receiving oral or parenteral methotrexate (MTX) for at least 12 weeks and been on a stable dose and route of MTX between 10 to 25 mg/week for at least 8 weeks prior to the first administration of the study drug.
Patients who had previously received targeted synthetic DMARD(s) for the treatment of RA and/or an IL-6 inhibitor for any purposes or rituximab or more than 1 biologic agents approved for the treatment of RA were excluded. A patient with 1 biologic agent for the treatment of RA could be enrolled after sufficient wash-out period of at least 3 months or 5 half-lives (whichever was longer) prior to the first

administration of the study drug (Day 1), except for etanercept and anakinra where only a 1-month washout prior to the first administration of study drug (Day 1) was necessary. Some conventional DMARDs, e.g. sulfasalazine, were allowed as prior medication.

- **Treatments**

The study comprised of 3 periods including screening period, Treatment Periods (I and II), and EOS visit (**Figure 5**).

Screening Period (**Day -42 to Day -1**): Screening took place between day -42 and day -1 (6 weeks), prior to the first study drug administration.

Treatment Period (**Week 0 to prior to Week 52**):

- Treatment Period I (from week 0 [day 1] to Week 24 predose)
- Treatment Period II (from week 24 to prior to Week 52 [EOS visit])

During Treatment Periods (I and II), patients received either CT-P47 or RoActemra 8 mg/kg (not exceeding 800 mg/dose) by IV infusion at every 4 weeks (Q4W), as per first and second randomisation. The patients were co-administered with MTX between 10 to 25 mg/week, oral or parenteral dose (IM or SC; dose and route were maintained from beginning to EOS) and folic acid (≥5 mg/week, oral dose).

Rescue therapy

From Week 16 and thereafter, patients who had less than 20% improvement in both swollen and tender joint counts compared to baseline could receive rescue treatment at the discretion of the investigator by initiating or increasing background RA medications (including those prohibited by the protocol). Aside from MTX and folic acid, patients were permitted to receive either oral or parenteral glucocorticoids (≤10 mg daily of prednisone/prednisolone or equivalent), and NSAID, if they had received a stable dose for at least 4 weeks prior to the first administration of the study drug (Day 1) and the same dose had to be maintained until 24 weeks after the first administration of the study drug (Day 1). In addition, patients were permitted to receive low potency topical, inhaled, otic, and ophthalmic glucocorticoid preparations. The information about the rescue therapy used were reported in the patient's eCRF. The patient was to be discontinued from the study drug and treated according to standard of care and at the discretion of the investigator. Patients receiving rescue treatment were to be attended all visits until Week 52.

- **Objectives**

The primary objective of the study was to demonstrate that CT-P47 is equivalent to EU-RoActemra in terms of efficacy as determined by clinical response according to the change from baseline in disease activity measured by DAS28 (ESR) at Week 12 in subjects with moderate to severe active RA assigned to CT-P47 and a stable dose of methotrexate, compared to the group assigned to EU-RoActemra and a stable dose of methotrexate.

The primary population of primary endpoint was the intention-to-treat (ITT) Set evaluated under a treatment policy estimand. All available data was included in the primary analysis regardless of intercurrent events such as study drug discontinuation, switch to rescue therapy or protocol violation. A supportive analysis for the primary efficacy endpoint was conducted using the per-protocol set (PPS).

Secondary objective

Secondary Objective of the study was to evaluate additional efficacy, PK, and overall safety, including immunogenicity, analysed descriptively without control for multiplicity.

The secondary efficacy endpoints, PK endpoint and safety endpoints were evaluated under a treatment policy estimand. For the treatment policy estimand, all available data were included in the analysis regardless of intercurrent events such as study drug discontinuation, switch to rescue therapy or protocol violation.

- **Outcomes/endpoints**

Primary endpoint

The primary efficacy endpoint is the change from baseline in DAS28(ESR) at Week 12. The DAS28(ESR) score is a conventional method for describing severity of rheumatoid arthritis using clinical and laboratory data, specifically erythrocyte sedimentation rate (ESR), Tender Joint Count (0-28), SJC28 = Swollen Joint Count (0-28), and patient's global disease activity measured on VAS (0-100 mm) (GH). The calculation method of DAS28(ESR) is not included here for brevity.

DAS28(ESR) is endorsed by the European League Against Rheumatism (EULAR) and other official rheumatology bodies in guiding the direction of the effect and ensuring that an early indication in disease improvement has been appropriately captured. The applicant states that since DAS28(CRP) can be influenced by tocilizumab alone due to presence of IL-6 binding site in CRP gene, DAS28(ESR) was chosen as primary endpoint to decrease IL-6 direct inhibition.

Secondary endpoints

The following secondary efficacy endpoints are assessed up to Week 52:
- ACR20, ACR50 and ACR70
- Individual components of the ACR (Number of tender and swollen joints with a total of 68 joints assessed for tenderness and 66 for swelling; Patient's and physician's global assessment of disease activity measured on visual analogue scale (VAS); Patient's assessment of pain measured on visual analogue scale (VAS); Health Assessment Questionnaire (HAQ) estimate of physical ability; CRP and ESR
- Hybrid ACR response
- DAS28 (CRP)
- DAS28 (ESR) (except for Week 12)
- Individual components of the DAS28
- EULAR response
- Simplified disease activity index (SDAI) and clinical disease activity index (CDAI)
- ACR/EULAR remission (Boolean-based definition)
- 36-item short form health survey (SF-36)
- Joint damage progression based on radiographic evaluations

Pharmacokinetic Assessment:

- Serum tocilizumab concentration at each time point up to Week 52

Safety Assessments:

Safety assessments are performed on AEs (including serious AEs), AEs of special interest (AESI) (infection, hypersensitivity including anaphylaxis, hepatic event, haemorrhage, gastrointestinal perforation, malignancy, and demyelinating disorder), immunogenicity, hypersensitivity monitoring (via monitoring of vital signs, includes BP, heart and respiratory rates, and body temperature), vital sign and weight measurement, ECGs, physical examination findings, IGRA, chest X-ray, hepatitis B and hepatitis C and HIV status, pregnancy testing, clinical laboratory analyses, signs and symptoms of TB, and prior and concomitant medications monitored throughout the study.

- **Sample size**

A sample size of 336 patients (168 patients in each treatment group of CT-P47 and RoActemra) resulted in at least 90% statistical power to demonstrate equivalence of CT-P47 and RoActemra based on the two-sided 95% confidence interval for the difference of mean change from baseline of DAS28 (ESR) score at Week 12. In the sample size calculation, equivalence margin of ±0.6, two one-sided 2.5% significance level, standard deviation of 1.43 and actual difference of 0 in mean change from baseline at Week 12 were assumed. The drop-out rate was hypothesised at 25%; therefore, approximately 448 patients (224 patients in each treatment group of CT-P47 and RoActemra) were to be randomised. The sample size with sufficient number of patients remaining at the time of single transition was also considered.

- **Randomisation and Blinding (masking)**

An interactive web response system (IWRS) was used for the randomisation. Unblinded biostatistician generated the randomisation schedule for IWRS, which linked sequential patient randomisation numbers to treatment codes. The randomisation numbers were blocked, and within each block the pre-specified ratio of patients was allocated to each treatment group. The block size was not revealed.

On Day 1 (Week 0), patients who met all the inclusion criteria and none of the exclusion criteria were enrolled in the study and randomly assigned to receive either CT-P47 or RoActemra prior to treatment using a 1:1 allocation ratio.

Prior to dosing at Week 24, all patients underwent the second randomisation process. Patients who were initially randomised to RoActemra were randomised again in a ratio of 1:1 to either continue with RoActemra or undergo transition to CT-P47. Patients who were randomised to CT-P47 or RoActemra received the assigned study drug Q4W from Week 24 and thereafter up to Week 48.

Stratification

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

- Body weight (<100 kg or ≥100kg) measured on Day 1
- Disease activity by DAS28 (ESR) score at Screening (>5.1 or ≤5.1)
- Prior biologic use approved for RA treatment (yes or no)

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

- Disease activity by DAS28 (ESR) score at Week 20; <2.6 vs ≥2.6

Unblinding

The blind was to be broken only if specific emergency treatment was dictated, as knowing the study drug assignment was required for medical management. In such cases, the investigator could, in an emergency, determine the identity of the study drug by using the applicable procedure in the IWRS.

The study was unblinded for reporting after completion of Week 32 of all patients and efficacy, PK, and safety endpoints were evaluated by predefined unblinded sponsor teams. The investigators, patients, and predefined CELLTRION and contract research organisation-blinded teams remain blind until the end of the study.

- **Statistical methods**

The difference of mean change from baseline of DAS28 (ESR) score at Week 12 was analysed using an analysis of covariance model with treatment as a fixed effect and body weight (<100 kg or ≥100 kg) measured on Day 1, disease activity by DAS28 (ESR) score at baseline (continuous value), and prior biologic use approved for RA treatment (yes or no) as covariates.

The two-sided 95% confidence interval (CI) for the difference between the 2 treatment groups (CT-P47 and RoActemra) was produced. Therapeutic equivalence of treatment difference in the change from baseline of DAS28 (ESR) at Week 12 by the ANCOVA analysis was concluded if the 95% CIs for the treatment difference was entirely within –0.6 to 0.6.

The primary population of primary endpoint was the intention-to-treat (ITT) set evaluated under a treatment policy estimand. The ITT set was defined as all patients randomly assigned to receive study drugs (CT-P47 or RoActemra) at Day 1 (Week 0). For the treatment policy estimand, all available data was included in the primary analysis regardless of intercurrent events such as study drug discontinuation, switch to rescue therapy or protocol violation. A supportive analysis for the primary efficacy endpoint was conducted using the per-protocol set (PPS). The PPS was defined as all randomly assigned patients who were compliant with therapy (defined to be ≥80% of planned cumulative doses up to Week 8) and had a DAS28 (ESR) assessment at baseline and Week 12 and did not have any major protocol deviation affecting primary efficacy endpoint. Additionally, sensitivity analysis to evaluate the impact of missing data was conducted on the ITT set by imputing missing data and using tipping point approach. The secondary efficacy endpoints were descriptively summarised using the ITT set and PPS.

No adjustment for multiplicity was defined and no interim analyses were planned for this study.

Results

A total of 556 patients were screened. Of these, 85 patients were excluded from the study due to screening failure; the most frequently reported reason for screening failure was inclusion/exclusion criteria not met (71 patients). In total, 471 patients from 22 study centres in Poland were enrolled in this study:

- 234 patients were randomly assigned to CT-P47 group
- 237 patients were randomly assigned to European Union (EU)-approved RoActemra group.

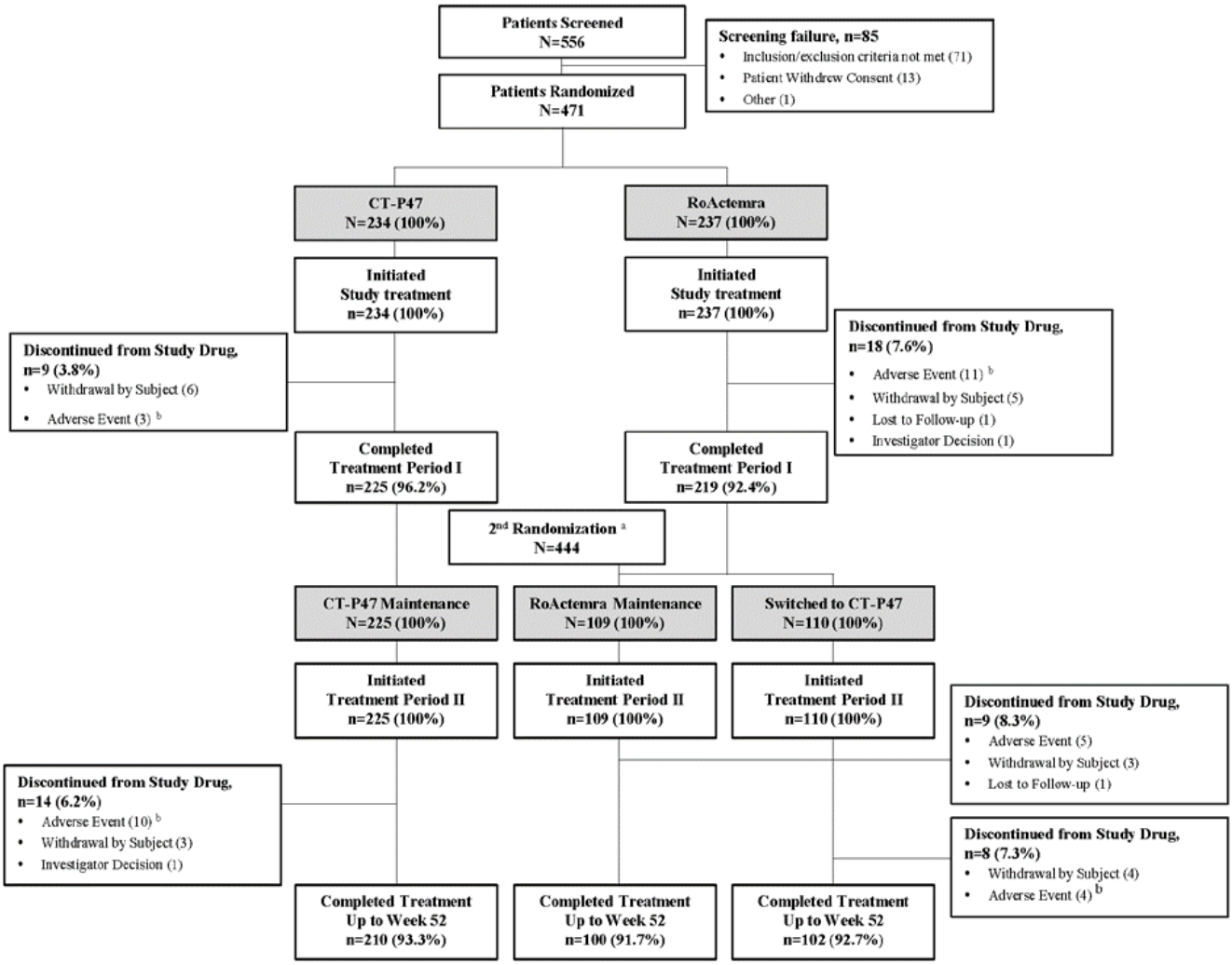
The discontinuation rate was low in the CT-P47 group by the end of TP I (3.8%) and higher in the RoActemra group (7.6%). The leading reason for discontinuation were AEs followed by the withdrawal by patients. In period II, discontinuation rates were low (below 2%) in both arms, and they were mainly due to AEs.

In Treatment Period II, 444 patients were randomly assigned to study drug and initiated the study treatment (225 [100%] patients, 109 [100%] patients, and 110 [100%] patients in the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups, respectively).

Of the 444 patients, 31 (7.0%) patients discontinued the study drug (14 [6.2%], 9 [8.3%], and 8 [7.3%] patients in the CT-P47 maintenance, RoActemra maintenance, and Switched to CT-P47 groups, respectively). In total, the reported primary reasons for study drug discontinuation were adverse event (AE) (4.3%), withdrawal by subject (2.3%), lost to follow-up (0.2%), and investigator decision (0.2%). (

Figure *6*).

- **Participant flow**



Abbreviations: Q4W, every 4 weeks
[a] Prior to dosing at Week 24, all patients underwent a second randomisation process. Patients who were initially randomised to RoActemra were randomised again in a ratio of 1:1 to either continue with RoActemra or undergo transition to CT-P47. Patients who were randomised to CT-P47 or RoActemra received assigned study drug Q4W from Week 24 and thereafter up to Week 48.
[b] The numerical difference between patients who discontinued from the study drug due to AE in patient disposition and summary of TEAE leading to study drug discontinuation is due to the fact that patient disposition's summary was based on the number of patients discontinued in each treatment period (and Week 32 cut-off date was also applied) and the summary of TEAE leading to discontinuation was based on the start date of AE.

Figure 6 Summary of patient disposition (treatment period I and treatment period II): ITT set and ITT-treatment period II subset

- **Recruitment**

The study was initiated on 14 Sep 2022 (first patient randomly assigned to treatment). The study was completed on 23 Nov 2023 (last patient Week 52 visit). Screening took place between day -42 and day -1 (6 weeks), prior to the first study drug administration.

- **Conduct of the study**

The original protocol (1.0) was dated 13 Apr 2022. The protocol was amended three times: on 27 Apr 2022, 07 Jul 2022, and 7 Jul 2022. None of the protocol versions include any list of specific amendments performed for the version. All protocol versions were dated prior to study initiation date (14 Sep 2022, when first patient was randomly assigned to treatment).

There was no change in the conduct of the study or planned analyses instituted after the start of the study except for below:

1. Number of Multiple Imputation (MI) Iterations

According to study protocol, planned number of MI iterations was 10. However, the number of MI iterations was increased to 100 because more reliable estimation was possible as the number of iterations increased.

2. Covariate for Primary Efficacy Endpoint

In the protocol, stratification factors were covariates of the primary efficacy analysis, but one of the stratification factors "Disease Activity by DAS28 (ESR) score at Screening (>5.1 or ≤5.1) (categorical value) was changed to "Baseline DAS28 (ESR) score (continuous value)" according to the CHMP guideline "Guideline on adjustment for baseline covariates in clinical trials (EMA/CHMP/295050/2013)".

There were no major protocol deviations which may affect the interpretation of study results of primary efficacy endpoint. Other reasons for exclusion from analysis sets in Treatment Periods I and II are given in Tables 32 and 33.

Table 32 Other reasons for exclusion from analysis set (treatment period I): ITT set

	CT-P47 (N=234)	RoActemra (N=237)	Total (N=471)	Excluded Analysis Sets
	Number (%) of patients			
Other Reasons for Exclusion				
Did not have a DAS28 (ESR) assessment at Week 12 [a]	13 (5.6)	12 (5.1)	25 (5.3)	PPS
Non-compliant with therapy (defined to be ≥80% of planned cumulative doses up to Week 8) [a]	12 (5.1)	23 (9.7)	35 (7.4)	PPS
Did not perform 2nd randomization at Week 24	9 (3.8)	18 (7.6)	27 (5.7)	ITT2
Did not receive at least 1 dose (full or partial) of study drug (CT-P47 or RoActemra) at or after Week 24	9 (3.8)	18 (7.6)	27 (5.7)	SAF2

Abbreviations: ITT, Intent-to-Treat; ITT2, ITT-Treatment Period II subset; PPS, per-protocol Set; SAF2, Safety-Treatment Period II subset.

[a] A total of 9 (1.9%) (CT-P47: 4 [1.7%] and RoActemra: 5 [2.1%]) patients met both criteria of did not have a DAS28 (ESR)assessment at Week 12 and non-compliant with therapy (defined to be ≥80% of planned cumulative doses up to Week 8).

Table 33 Other reasons for exclusion from analysis subset (treatment period II): ITT-treatment period II subset

	CT-P47 Maintenance (N=225)	RoActemra Maintenance (N=109)	Switched to CT-P47 (N=110)	Total (N=444)	Excluded Subset
	Number (%) of patients				
Other reasons for exclusion					
Did not have at least 1 post-treatment PK concentration data at or after Week 24	1 (0.4)	1 (0.9) [a]	1 (0.9)	3 (0.7)	PK2
Did not receive at least 1 full 8 mg/kg dose of study drug at or after Week 24	17 (7.6)	12 (11.0) [a]	9 (8.2)	38 (8.6)	PK2

Abbreviations: ITT, intent-to-treat; PK2, pharmacokinetic set – Treatment Period II subset.
[a] One patient in the RoActemra maintenance group met both criteria of did not have at least 1 post-treatment PK concentration data at or after Week 24 and did not receive at least 1 full 8 mg/kg dose of study drug at or after Week 24
.

- **Baseline data**

Baseline demographic, disease and treatment characteristics by treatment group are provided in **Table 34** for the ITT Set and in

Table 35 for the ITT-Treatment Period II Subset. The age range was wide (20-73 years). The smaller proportion of male vs. female patients (110 [23.4%]) reflects the prevalence of RA in general population. All patients were white, of which 10 Hispanic/Latino.

The majority of patients had high disease activity based on DAS28 (ESR) score (DAS28 [ESR] >5.1) at Screening (229 [97.9%] patients in the CT-P47 group and 230 [97.0%] patients in the RoActemra group). The proportion of subjects with use of 1 prior biologic approved for RA treatment was evenly divided (24.8% and 26.2% in the CT-P47 and RoActemra groups, respectively). In the TP II subset, disease activity by ACR revised criteria at Screening was similarly high and comparable across the CT-P47 maintenance, RoActemra maintenance, and Switched to CT-P47 groups, respectively: a functional status of Class I in 6.2%, 12.8% and 9.1% or subjects; Class II in 85.8%, 74.3%, and 80% of subjects, Class III in 8%, 12.8% and 10.9% of subjects; and Class IV in none of the subjects.

Throughout the entire study period, no patients were identified as being infected with HBV, HCV, and HIV. There were a total of 3 patients who had either positive or unsettled hepatitis C antibody test result at baseline. The HCV Ribonucleic acid (RNA) test was not planned per protocol, but the RNA test was performed for these patients, and all were included in the study based on negative HCV RNA results. There were 45 patients with positive hepatitis B core antibody (26 [11.1%] patients in the CT-P47 and 19 [8.0%] patients in the RoActemra groups) at baseline. The HBV DNA tests were performed for these patients, and all were enrolled in the study based on negative HBV DNA test results.

Table 34 Demographics and stratification details: ITT set

	CT-P47 (N=234)	RoActemra (N=237)	Total (N=471)
Age (years)			
n	234	237	471
Mean (SD)	55.1 (10.98)	54.4 (11.61)	54.8 (11.3)
Median	57.0	55.0	56.0
Min, max	20, 73	22, 73	20, 73
Gender, n (%)			
Male	53 (22.6)	57 (24.1)	110 (23.4)
Female	181 (77.4)	180 (75.9)	361 (76.6)
Female fertility status [a], n (%)			
Surgically sterilized	5 (2.8)	6 (3.3)	11 (3.0)
Post-menopausal	118 (65.2)	110 (61.1)	228 (63.2)
Potentially able to bear children	58 (32.0)	64 (35.6)	122 (33.8)
Race, n (%)			
White	234 (100)	237 (100)	471 (100)
Ethnicity, n (%)			
Hispanic or Latino	6 (2.6)	4 (1.7)	10 (2.1)
Non-Hispanic or Non-Latino	228 (97.4)	233 (98.3)	461 (97.9)
Screening Height (cm)			
n	234	237	471
Mean (SD)	165.83 (8.694)	166.16 (8.667)	165.99 (8.673)
Median	165.50	165.50	165.50
Min, max	144, 197	146, 193	144, 197
Screening Weight (kg)			
n	234	237	471
Mean (SD)	76.68 (16.826)	75.51 (17.771)	76.09 (17.300)
Median	74.90	72.00	73.70
Min, max	39, 131.5	45, 149.7	39, 149.7
Body Weight on Day 1, n (%)			
<100 kg	208 (88.9)	210 (88.6)	418 (88.7)
≥100 kg	26 (11.1)	27 (11.4)	53 (11.3)
DAS28 (ESR) score at Screening, n (%)			
DAS28 (ESR) >5.1	229 (97.9)	230 (97.0)	459 (97.5)
DAS28 (ESR) ≤5.1	5 (2.1)	7 (3.0)	12 (2.5)
Prior biologic use approved for RA treatment, n (%)			
Yes	58 (24.8)	62 (26.2)	120 (25.5)
No	176 (75.2)	175 (73.8)	351 (74.5)

Abbreviations: DAS28, Disease Activity Score using 28 joint counts; ITT, intent-to-treat; max, maximum; min, minimum; RA, rheumatoid arthritis; SD, standard deviation.

[a] Percentages were calculated by using the number of female patients as the denominator.

Table 35 Demographics and stratification details: ITT-treatment period II subset

	CT-P47 Maintenance (N=225)	RoActemra Maintenance (N=109)	Switched to CT-P47 (N=110)	Total (N=444)
Age (years)				
n	225	109	110	444
Mean (SD)	55.2 (10.96)	55.6 (11.39)	53.4 (11.70)	54.9 (11.26)
Median	57.0	57.0	54.0	56.5
Min, max	20, 73	27, 73	22, 73	20, 73
Gender, n (%)				
Male	49 (21.8)	35 (32.1)	21 (19.1)	105 (23.6)
Female	176 (78.2)	74 (67.9)	89 (80.9)	339 (76.4)
Female fertility status [a], n (%)				
Surgically sterilized	5 (2.8)	3 (4.1)	3 (3.4)	11 (3.2)
Post-menopausal	115 (65.3)	47 (63.5)	51 (57.3)	213 (62.8)
Potentially able to bear children	56 (31.8)	24 (32.4)	35 (39.3)	115 (33.9)
Race, n (%)				
White	225 (100)	109 (100)	110 (100)	444 (100)
Ethnicity, n (%)				
Hispanic or Latino	6 (2.7)	3 (2.8)	1 (0.9)	10 (2.3)
Non-Hispanic or Non-Latino	219 (97.3)	106 (97.2)	109 (99.1)	434 (97.7)
Screening Height (cm)				
n	225	109	110	444
Mean (SD)	165.56 (8.503)	167.02 (8.794)	165.23 (8.393)	165.83 (8.557)
Median	165.00	166.00	165.00	165.00
Min, max	144, 188	149, 188	146, 188	144, 188
Screening Weight (kg)				
n	225	109	110	444
Mean (SD)	76.70 (16.943)	75.85 (18.037)	75.48 (18.342)	76.19 (17.537)
Median	75.00	72.00	72.00	73.60
Min, max	39, 131.5	45.5, 149.7	45, 135.9	39, 149.7
Body Weight on Day 1, n (%)				
<100 kg	200 (88.9)	95 (87.2)	98 (89.1)	393 (88.5)
≥100 kg	25 (11.1)	14 (12.8)	12 (10.9)	51 (11.5)
DAS28 (ESR) score at Screening, n (%)				
DAS28 (ESR) >5.1	220 (97.8)	108 (99.1)	105 (95.5)	433 (97.5)
DAS28 (ESR) ≤5.1	5 (2.2)	1 (0.9)	5 (4.5)	11 (2.5)
Prior biologic use approved for RA treatment, n (%)				
Yes	55 (24.4)	25 (22.9)	33 (30)	113 (25.5)
No	170 (75.6)	84 (77.1)	77 (70)	331 (74.5)
DAS28 (ESR) score at Week 20, n (%)				
DAS28 (ESR) <2.6	124 (55.1)	60 (55.0)	62 (56.4)	246 (55.4)
DAS28 (ESR) ≥2.6	101 (44.9)	49 (45.0)	48 (43.6)	198 (44.6)

Abbreviations: DAS28, Disease Activity Score using 28 joint counts; ESR, erythrocyte sedimentation rate; ITT, intent-to-treat; max, maximum; min, minimum; RA, rheumatoid arthritis; SD, standard deviation.
[a] Percentages were calculated by using the number of female patients as the denominator.

After re-randomisation, the mean age of subjects was ≈3 years lower in the Switched to CT-P47 group

than in the CT-P47 Maintenance and RoActemra Maintenance groups; and the proportion of postmenopausal women was accordingly lower in this group. After re-randomisation, the proportion of men was higher in the RoActemra group than in the CT-P47 Maintenance and Switched to CT-P47 groups (**Table 35**). These small differences were not deemed to affect comparative efficacy results.

- **Numbers analysed**

See Table 32 and 44 for reasons why subjects were excluded from different analysis sets for Treatment Period I and II.

All enrolled patients in the CT-P47 and RoActemra groups were included in the ITT set and safety analysis set for Treatment Period I (**Table 36**).

Table 36 Treatment period I, analysis sets

	CT-P47	RoActemra	Total
Intent-to-Treat Set	234	237	471
Per-Protocol Set	213	207	420
Pharmacokinetic Set	234	237	471
Safety Set	234	237	471

Note: The actual treatments were used for PK and Safety Sets.

In total, 27/471 subjects (9 in the CT-P47 group) did not perform 2nd randomisation at Week 24 and were not included in the ITT-Treatment Period II and safety analysis sets. Altogether 444 patients were included in the ITT-Treatment Period II subset (225 patients, 109 patients and 110 patients in the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups, respectively). The proportion of patients in each of the other analysis subsets was similar among the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups (**Table 37**).

Table 37 Treatment period II, analysis subsets

	CT-P47 Maintenance	RoActemra Maintenance	Switched to CT-P47	Total
ITT-Treatment Period II subset	225	109	110	444
PK-Treatment Period II subset	207	97	100	404
Safety-Treatment Period II subset	225	109	110	444

Abbreviations: ITT, intent-to-treat; PK, pharmacokinetics.

Note: The actual treatments were used for PK-Treatment Period II and Safety-Treatment Period II subsets.

- **Outcomes and estimation**

Primary endpoint

The primary population for the summary of primary endpoint was ITT set under a treatment policy estimand.

The primary efficacy endpoint was the mean change from baseline in DAS28 (ESR) at Week 12 and the ANCOVA for the change from baseline of DAS28 (ESR) at Week 12. Results of the primary endpoint are given in **Table 38**. The 95% CIs for the estimate of treatment difference in change from baseline of

DAS (ESR) at Week 12 were entirely within the equivalence margin of -0.6 to 0.6 in both ITT and PP Sets: 95% CI: [-0.26, 0.24] in the ITT Set and 95% CI: [-0.20, 0.29] in PPS.

Table 38 Analysis of change from baseline of DAS28 (ESR) at week 12 (ANCOVA): ITT set and PPS

Treatment Group	n	LS Mean (SE)	Estimate of Treatment Difference	95% CI of Treatment Difference
ITT Set				
CT-P47	221	-3.01 (0.121)	-0.01	(-0.26, 0.24)
EU-RoActemra	225	-3.00 (0.120)		
PPS				
CT-P47	213	-3.05 (0.121)	0.04	(-0.20, 0.29)
EU-RoActemra	207	-3.09 (0.119)		

Note: An ANCOVA comparing the mean change from baseline of DAS28 (ESR) at Week 12 between two treatment groups, CT-P47 and RoActemra, was conducted considering the treatment as fixed effect, and body weight (<100 kg or ≥100 kg) measured on Day 1, baseline DAS28 (ESR) score and prior biologic use approved for RA treatment (yes or no) as covariates.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; DAS, disease activity score; ESR, erythrocyte sedimentation rate; ITT, intent-to-treat; LS, least squares; PPS, per-protocol set; RA, rheumatoid arthritis; SE, standard error.

Sensitivity analysis using the ANCOVA with multiple imputation (MI) for the change from baseline of DAS28(ESR) at Week 12 for the ITT set indicated therapeutic equivalence between the groups (table 3.3.4.8). The results from ANCOVA in the PPS were also found to be equivalent between the 2 groups (95% CI: [-0.20, 0.29]).

Table 39 Analysis of change from baseline of DAS28(ESR) at week 12 (ANCOVA)

Treatment Group	n	LS Mean (SE)	Estimate of Treatment Difference	95% CI of Treatment Difference
ITT Set				
CT-P47	234	-3.01 (0.122)	-0.01	(-0.25, 0.24)
EU-RoActemra	237	-3.00 (0.121)		

Note. Missing values in the change from baseline of DAS28 (ESR) at Week 12 were imputed using regression method with treatment, body weight (<100 kg or ≥100 kg) measured on Day 1, baseline DAS28 (ESR) score, and prior biologic use approved for RA treatment (yes or no) as covariates. The 100 imputed datasets were created. An ANCOVA comparing the change from baseline of DAS28 (ESR) at Week 12 between two treatment groups, CT- P47 and RoActemra, were conducted considering the treatment as fixed effect, and body weight (<100 kg or ≥100 kg) measured on Day 1, baseline DAS28 (ESR) score, and prior biologic use approved for RA treatment (yes or no) as covariates. The 100 complete datasets were analysed by ANCOVA, results from each set of imputed datasets were then be pooled using Rubin's method. A total of 13 patients and 12 patients in the CT-P47 and RoActemra groups, respectively, with missing DAS28 (ESR) score at Week 12 were imputed.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; DAS, disease activity score; ESR, erythrocyte sedimentation rate; ITT, intent-to-treat; LS, least squares; MI, multiple imputation; RA, rheumatoid arthritis; SE, standard error.

Sensitivity analysis with Multiple imputation (MI) under the Missing At Random (MAR) assumption for missing data handling and tipping point analysis under the Missing Not At Random (MNAR) assumption were conducted on the ITT Set in order to assess the robustness of the primary efficacy analysis or the impact of missing data.

The number of patients with missing value in the mean change from baseline in DAS28 (ESR) at Week 12 were 25 patients and distributed similarly between the CT-P47 group and EU-RoActemra groups (13 [5.6%] and 12 [5.1%] patients, respectively*).* The results of the tipping point analysis indicate that the primary efficacy endpoint was robust to missing data (data not shown for brevity).

Secondary efficacy endpoints

All analyses for the secondary efficacy endpoints were conducted on the ITT and PP Sets (Treatment period I) and on its corresponding subset (ITT – Treatment Period II subset).

Mean change from DAS28(ESR/CRP)

The mean change in DAS28 score (ESR/CRP) from baseline at Weeks 12 and 24 (Treatment Period I) for the ITT Set and Weeks 24 and 32 and 52 (Treatment Period II) for the ITT–Treatment Period II subset are summarised in **Table 40** and **Figure 7**.

Table 40 Descriptive statistics for actual value and change from baseline of DAS28 (ESR/CRP) (ITT set and ITT-treatment period II subset).

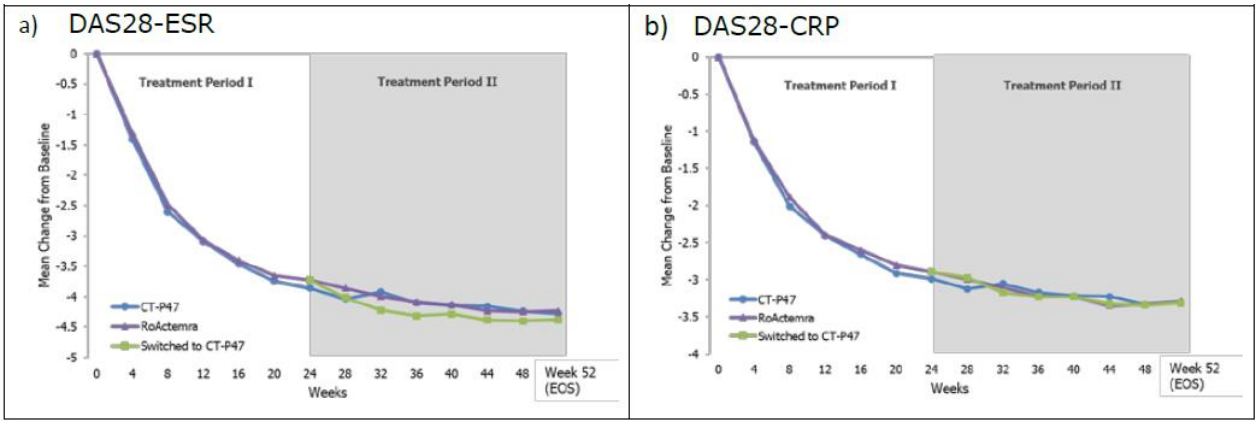
Visit Statistic	CT-P47 (N=234)	RoActemra (N=237)	
	Change From Baseline		
DAS28 (ESR)			
Baseline [a] Mean (SD)	6.426 (0.6197)	6.364 (0.7048)	
Week 12 [b] Mean (SD)	-3.091 (1.3174)	-3.070 (1.3351)	
Week 24 [b] Mean (SD)	-3.858 (1.2402)	-3.720 (1.3945)	
Visit Statistic	**CT-P47 Maintenance (N=225)**	**RoActemra Maintenance (N=109)**	**Switched to CT-P47 (N=110)**
Week 24 [b] Mean (SD)	-3.868 (1.2344)	-3.702 (1.3875)	-3.846 (1.3369)
Week 32 [b] Mean (SD)	-3.921 (1.2548)	-3.994 (1.1753)	-4.218 (1.1380)
Week 52 (EOS) [b] Mean (SD)	-4.279 (1.1934)	-4.231 (1.3046)	-4.376 (1.4212)
Visit Statistic	**CT-P47 (N=234)**	**RoActemra (N=237)**	
	Change From Baseline		
DAS28 (CRP)			
Baseline [a] Mean (SD)	5.510 (0.7422)	5.451 (0.8124)	
Week 12 [b] Mean (SD)	-2.404 (1.1067)	-2.392 (1.1350)	
Week 24 [b] Mean (SD)	-2.989 (1.0776)	-2.889 (1.2039)	
Visit Statistic	**CT-P47 Maintenance (N=225)**	**RoActemra Maintenance (N=109)**	**Switched to CT-P47 (N=110)**
Week 24 [b] Mean (SD)	-2.996 (1.0759)	-2.900 (1.1998)	-2.941 (1.1892)
Week 32 [b] Mean (SD)	-3.050 (1.1131)	-3.104 (1.0427)	-3.171 (1.0769)
Week 52 (EOS) [b] Mean (SD)	-3.301 (1.0894)	-3.285 (1.2394)	-3.306 (1.2559)

Abbreviations: CRP, C-reactive protein; DAS28, Disease Activity Score using 28 joint counts; ESR; erythrocyte sedimentation rate; ITT, intent-to-treat; SD, standard deviation

[a] For the baseline value, actual results were presented.

[b] For Weeks 12, 24 and 32 and 52 (EOS) values, change from baseline results were presented.

The actual value of DAS28 (ESR) at Week 52 was similar across study groups: the mean (SD) was 2.160 (1.1987), 2.115 (1.2952) and 1.98 (1.3386) in the CT-P47 Maintenance, RoActemra Maintenance and Switched to CT-P47 groups, respectively. Hence, a majority of patients had low disease activity [DAS28 (ESR) 2.6-3.2] or remission [DAS28 (ESR) <2.6], even though results have not been submitted as categorised for actual values of DAS28 (ESR).



Abbreviations: CRP, C-reactive protein; DAS28, Disease Activity Score 28; ESR, Erythrocyte sedimentation rate; EOS, End of study.

Figure 7 Mean change from baseline of DAS28 (ESR/CRP) up to Week 52 – ITT set & ITT treatment Period II subset

Individual components of DAS28 comparison with baseline

During TP I, there were decreases in mean scores for each individual DAS28 component (tender/swollen joint counts [DAS28 assessment], VAS scores for patient's global assessment of disease activity, CRP and ESR) in each treatment groups for the ITT set. The mean changes from baseline of each individual DAS28 component were comparable between the CT-P47 and EU-RoActemra groups at Week 24 (data not shown for brevity).

During TP II, the mean changes from baseline of each individual DAS28 component were generally maintained with a slight increasing trend among the CT-P47 maintenance, EU-RoActemra maintenance, and Switched to CT-P47 groups for the ITT-Treatment Period II subset. The mean changes from baseline of each individual DAS28 component were comparable among the CT-P47 maintenance, EU-RoActemra maintenance and Switched to CTP47 groups (data not shown for brevity).

ACR20, ACR50 and ACR70 Responses

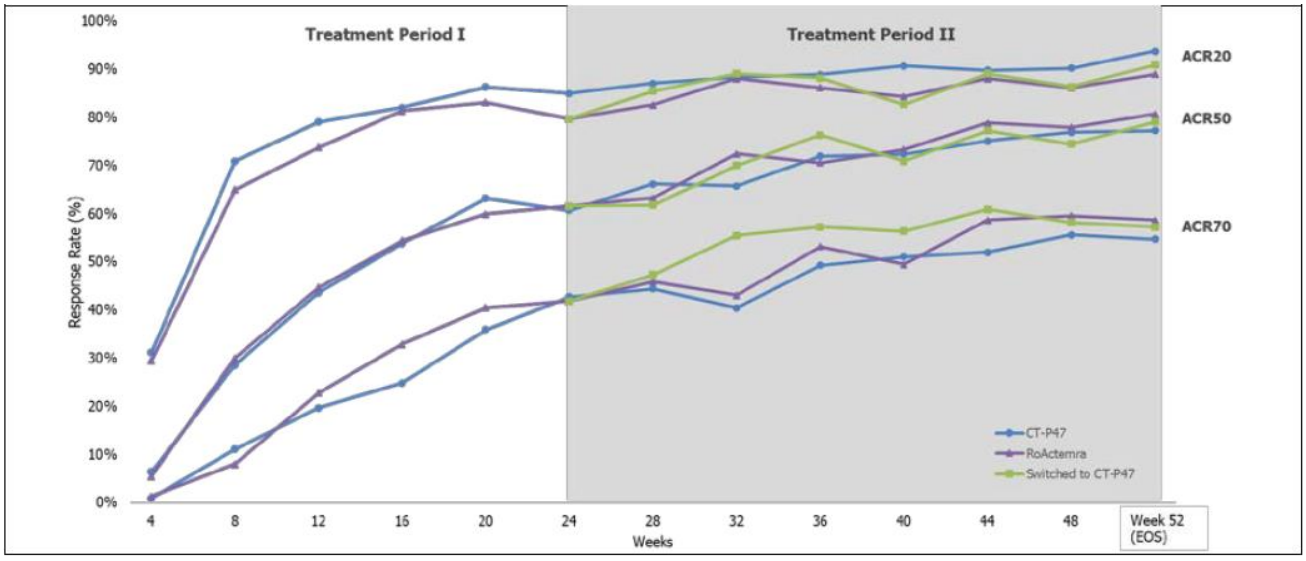
The proportions of patients achieving a clinical response according to the ACR20/50/70 criteria were generally similar among the treatment groups (**Table 41** and **Figure 8**).

Table 41 Proportion of patients achieving response according to ACR20/50/70 criteria in study CT-P47 3.1 (ITT set and ITT-treatment period II subset)

Visit Parameter	CT-P47 (N=234)	RoActemra (N=237)	
	Number (%) of patients		
Week 12			
ACR20	185 (79.1)	175 (73.8)	
ACR50	102 (43.6)	106 (44.7)	
ACR70	46 (19.7)	54 (22.8)	
Week 24			
ACR20	199 (85)	189 (79.7)	
ACR50	142 (60.7)	146 (61.6)	
ACR70	100 (42.7)	99 (41.8)	
Visit Parameter	**CT-P47 Maintenance (N=225)**	**RoActemra Maintenance (N=109)**	**Switched to CT-P47 (N=110)**

	Number (%) of patients		
Week 24			
ACR20	199 (88.4)	90 (82.6)	94 (85.5)
ACR50	142 (63.1)	69 (63.3)	74 (67.3)
ACR70	100 (44.4)	46 (42.2)	52 (47.3)
Week 32			
ACR20	199 (88.4)	96 (88.1)	98 (89.1)
ACR50	148 (65.8)	79 (72.5)	77 (70)
ACR70	91 (40.4)	47 (43.1)	61 (55.5)
Week 52 (EOS)			
ACR20	211 (93.8)	97 (89)	100 (90.9)
ACR50	174 (77.3)	88 (80.7)	87 (79.1)
ACR70	123 (54.7)	64 (58.7)	63 (57.3)

Abbreviations: ACR20, American College of Rheumatology definition of a 20% improvement criteria; ACR50, American College of Rheumatology definition of a 50% improvement criteria; ACR70, American College of Rheumatology definition of a 70% improvement criteria; EOS, end-of-study; ITT, intent-to-treat.
Note: Percentages were calculated using the number of patients in each set as the denominator.



Abbreviations: ACR20/50/70, American College of Rheumatology definition of a 20%/50%/70% improvement criteria; EOS, End of study.

Figure 8 Proportion of patients achieving ACR20/50/70% up to week 52 – ITT set & ITT treatment period II subset

Individual Components of the ACR Criteria Comparison with Baseline

The mean scores of each individual component of ACR 20, ACR50 and ACR70 (tender/swollen joint counts [ACR assessment], VAS scores for physician's global assessment of disease activity, health assessment questionnaire [HAQ] and CRP/ESR) in both treatment groups for the ITT Set decreased during Treatment Period I, and the mean changes were comparable between the CT-P47 and EU-RoActemra groups at Week 24. For the PP Set, similar results to that of the ITT Set were reported (data not shown for brevity).

During the Treatment Period II, the mean changes from baseline of each individual ACR component were generally maintained with a slight increasing trend among the CT-P47 maintenance, EU-

RoActemra maintenance, and Switched to CT-P47 groups for the ITT-Treatment Period II subset. The mean changes from baseline of each individual ACR component were comparable among the CT-P47 maintenance, EU-RoActemra maintenance and Switched to CTP47 groups. E.g., at W52 (EOS) in the CT-P47 Maintenance, RoActemra Maintenance, and Switched to CT-P47 groups (ITT – Treatment Period II subset), respectively, the mean change from baseline (cfb) in ESR was −30.1, −30,7 and −31.1 mm/h; the mean cfb for CRP at W52 was −7.25, −7.65 and −7.19 mg/L; and the Swollen Joint Count, the mean cfb was −11.7, −11.6, and −12.3 joints. Results for all individual components of ACR were similar across study groups throughout the study, and all results are not included here for brevity.

Hybrid ACR Response

The mean hybrid ACR scores are summarised by treatment group at Weeks 12 and 24 (Treatment Period I) for the ITT Set and Weeks 24, 32 and 52 (Treatment Period II) for the ITT–Treatment Period II subset in **Table 42**.

Table 42 Descriptive statistics for actual value of hybrid ACR Score in study CT-P47 3.1 (ITT set and ITT-treatment period II subset)

Visits, Statistics	**CT-P47 (N=234)**	**EU-RoActemra (N=237)**	
Week 12			
n	221	224	
Mean (SD)	51.920 (21.8811)	51.489 (23.7736)	
Week 24			
n	221	223	
Mean (SD)	62.391 (23.3237)	61.567 (25.1499)	
Visits, Statistics	**CT-P47 Maintenance (N=225)**	**EU-RoActemra Maintenance (N=109)**	**Switched to CT-P47 (N=110)**
Week 24			
n	220	107	108
Mean (SD)	62.617 (23.1329)	61.249 (25.7775)	63.356 (23.6615)
Week 32			
n	220	104	105
Mean (SD)	63.116 (22.6823)	66.225 (21.4135)	67.795 (21.5230)
Week 52 (EOS)			
n	219	102	106
Mean (SD)	70.107 (19.9605)	70.873 (22.6437)	71.145 (24.4396)

Abbreviations: ACR20, American College of Rheumatology; ITT, intent-to-treat; SD, standard deviation.

Proportion of Patients Achieving EULAR Response

The distribution of EULAR responses (good, moderate, and no responses) based on changes in DAS28 (CRP/ESR) from baseline by each scheduled visit are summarised in **Table 43** by treatment group at Weeks 12 and 24 (Treatment Period I) for the ITT Set and Weeks 24, 32 and 52 (Treatment Period II) for the ITT–Treatment Period II subset. Results are generally comparable.

For the PPS, similar results to that of the ITT Set were reported (data not shown for brevity).

Table 43 Summary of EULAR (CRP/ESR) criteria in study CT-P47 3.1 (ITT set and ITT-treatment period II subset)

EULAR (ESR)			
Visit, Response	**CT-P47 (N=234)**	**EU-RoActemra (N=237)**	
Week 12, n (%)			
No response	16 (6.8)	18 (7.6)	
Moderate response	100 (42.7)	95 (40.1)	
Good response	105 (44.9)	112 (47.3)	
Week 24, n (%)			
No response	4 (1.7)	6 (2.5)	
Moderate response	63 (26.9)	67 (28.3)	
Good response	155 (66.2)	150 (63.3)	
Visit, Response	**CT-P47 Maintenance (N=225)**	**EU-RoActemra Maintenance (N=109)**	**Switched to CT-47 (N=110)**
Week 24, n (%)			
No response	4 (1.8)	3 (2.8)	1 (0.9)
Moderate response	62 (27.6)	36 (33.0)	29 (26.4)
Good response	155 (68.9)	69 (63.3)	77 (70)
Week 32, n (%)			
No response	2 (0.9)	1 (0.9)	1 (0.9)
Moderate response	64 (28.4)	26 (23.9)	16 (14.5)
Good response	153 (68.0)	77 (70.6)	88 (80)
Week 52, n (%)			
No response	2 (0.9)	1 (0.9)	2 (1.8)
Moderate response	46 (20.4)	18 (16.5)	18 (16.4)
Good response	170 (75.6)	84 (77.1)	86 (78.2)
EULAR (CRP)			
Visit, Response	**CT-P47 (N=234)**	**EU-RoActemra (N=237)**	
Week 12, n (%)			
No response	11 (4.7)	12 (5.1)	
Moderate response	86 (36.8)	97 (40.9)	
Good response	124 (53.0)	116 (48.9)	
Week 24, n (%)			
No response	3 (1.3)	8 (3.4)	
Moderate response	61 (26.1)	50 (21.1)	
Good response	157 (67.1)	165 (69.6)	
Visit, Response	**CT-P47 Maintenance (N=225)**	**EU-RoActemra Maintenance (N=109)**	**Switched to CT-47 (N=110)**
Week 24, n (%)			
No response	3 (1.3)	3 (2.8)	3 (2.7)

Moderate response	60 (26.7)	25 (22.9)	23 (20.9)
Good response	157 (69.8)	80 (73.4)	81 (73.6)
Week 32, n (%)			
No response	5 (2.2)	1 (0.9)	1 (0.9)
Moderate response	51 (22.7)	17 (15.6)	18 (16.4)
Good response	164 (72.9)	87 (79.8)	86 (78.2)
Week 52, n (%)			
No response	3 (1.3)	3 (2.8)	1 (0.9)
Moderate response	37 (16.4)	13 (11.9)	20 (18.2)
Good response	179 (79.6)	88 (80.7)	85 (77.3)

Abbreviations: ACR20, American College of Rheumatology definition of a 20% improvement criteria; ACR50, American College of Rheumatology definition of a 50% improvement criteria; ACR70, American College of Rheumatology definition of a 70% improvement criteria; EULAR, European Alliance of Associations for Rheumatology; CRP, C-reactive protein; ESR; erythrocyte sedimentation rate; EOS, end-of-study; ITT, intent-to-treat. SD, standard deviation
Note: Percentages were calculated using the number of patients in each set as the denominator.

Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI)

The four parameters that are counted and summated in CDAI, are number of tender joints (TJC, 0–28), number of swollen joints (SJC, 0–28), patient global assessment of disease activity (PGA, on VAS) and evaluator/physician global assessment (EGA) of the disease activity of the disease activity (on VAS). SDAI is calculated as follows: SDAI = SJC + TJC +PGA + EGA + CRP. For CDAI, values are interpreted as follows: ≤2.8: remission, 2.8 and ≤10: low disease activity, 10 and ≤22: moderate disease activity, and >22: high disease activity. For SDAI, Remission is defined as an SDAI of <3.3, low disease activity as ≤11, moderate disease activity as ≤26 and high disease activity as >26.

At baseline, the mean actual values of CDAI for the ITT subset were 37.753 and 37.209 for the CT-P47 and Roactemra groups, respectively, and had decreased to a mean of 9.059 and 8.736 at Week 24, respectively. For SDAI, the actual values at baseline for the CT-P47 and Roactemra groups were 39.122 and 38.591, respectively; and at Week 24 the mean values were 9.269 and 9.306, respectively.

At Week 52 (end of study), the actual values of CDAI in the ITT TP II subset were 6.526, 6.159 and 6.208 for the CT-P47 Maintenance, RoActemra Maintenance and Switched to CT-P47 groups, respectively. For SDAI, the actual values at Week 52 were 6.808, 6.400 and 6.407 for the CT-P47 Maintenance, RoActemra Maintenance and Switched to CT-P47 groups, respectively (

Table *44*).

The mean changes from baseline in CDAI and SDAI are summarised by treatment group at Weeks 12 and 24 (Treatment Period I) for the ITT Set and Weeks 24, 32 and 52 (Treatment Period II) for the ITT–Treatment Period II subset in

Table *44*. The mean changes from baseline in CDAI and SDAI up to Week 52 were generally similar among the treatment groups.

For the PPS, similar results to that of the ITT Set were reported (data not shown for brevity).

Table 44 Descriptive statistics for actual value at baseline and change from baseline of CDAI and SDAI in study CT-P47 3.1 (ITT set and ITT-treatment period II subset)

CDAI			
Visit, Statistics	**CT-P47 (N=234)**	**EU-RoActemra (N=237)**	
	Change from baseline		
Baseline [a]			
Mean (SD)	38.005 (8.7412)	37.367 (10.3104)	
Week 12			
Mean (SD)	-23.824 (10.0876)	-23.834 (11.0612)	
Week 24			
Mean (SD)	-28.994 (9.0777)	-28.189 (11.2962)	
Visit, Statistics	**CT-P47 Maintenance (N=225)**	**EU-RoActemra Maintenance (N=109)**	**Switched to CT-P47 (N=110)**
	Change from baseline		
Week 24			
Mean (SD)	-29.022 (9.0880)	-28.552 (11.1850)	-28.524 (11.3879)
Week 32			
Mean (SD)	-29.745 (9.5362)	-30.053 (9.8226)	-30.242 (11.0376)
Week 52			
Mean (SD)	-31.666 (9.0311)	-31.076 (11.4076)	-31.041 (10.9124)
SDAI			
Visit, Statistics	**CT-P47 (N=234)**	**EU-RoActemra (N=237)**	
	Change from baseline		
Baseline [a]			
Mean (SD)	39.013 (9.2991)	38.339 (10.7781)	
Week 12			
Mean (SD)	-24.644 (10.4901)	-24.635 (11.4555)	
Week 24			
Mean (SD)	-29.890 (9.4994)	-28.926 (11.7366)	
Visit, Statistics	**CT-P47 Maintenance (N=225)**	**EU-RoActemra Maintenance (N=109)**	**Switched to CT-P47 (N=110)**
	Change from baseline		
Week 24			
Mean (SD)	-29.923 (9.5082)	-29.309 (11.6996)	-29.281 (11.7556)
Week 32			
Mean (SD)	-30.409 (10.1058)	-30.807 (10.3138)	-30.970 (11.2915)
Week 52			
Mean (SD)	-32.391 (9.6651)	-31.842 (11.9214)	-31.760 (11.3237)

Abbreviations: CDAI, clinical disease activity index; SDAI; simplified disease activity index; ITT, intent-to-treat; SD, standard deviation

[a] For the baseline value, actual results were presented

Proportion of Patients Achieving ACR/EULAR remission (Boolean-based definition)

The proportion of patients achieving ACR/EULAR remission (Boolean-based definition) were generally similar among the treatment groups. The results are summarised by treatment group at Weeks 12 and 24 (Treatment Period I) for the ITT Set and Weeks 24, 32 and 52 (Treatment Period II) for the ITT–Treatment Period II subset in **Table 45**.

For the PPS, similar results to that of the ITT Set were reported (data not shown for brevity).**Table 45 Proportion of patients achieving ACR/EULAR remission (Boolean-based definition) (ITT set and ITT-treatment period II subset)**

Visit	**CT-P47 (N=234)**	**EU-RoActemra (N=237)**	
	N (%) of patients		
Week 12	11 (4.7)	15 (6.3)	
Week 24	44 (18.8)	40 (16.9)	
Visit	**CT-P47 Maintenance (N=225)**	**EU-RoActemra Maintenance (N=109)**	**Switched to CT-P47 (N=110)**
	N (%) of patients		
Week 24	44 (19.6)	23 (21.1)	16 (14.5)
Week 32	53 (23.6)	21 (19.3)	31 (28.2)
Week 52	73 (32.4%)	35 (32.1%)	41 (37.3%)

Note: Percentages were calculated using the number of patients in each set as the denominator.
Abbreviations: ACR/EULAR, American College of Rheumatology/European Alliance of Associations for Rheumatology; ITT, intent-to treat

Health-Related Quality of Life (SF-36) Questionnaire

Actual values and change from baseline in all SF-36 subscales and component scores are summarised by treatment group at baseline, Weeks 12 and 24 (Treatment Period I) for the ITT Set and Weeks 24, 32 and 52 (Treatment Period II) for the ITT–Treatment Period II subset in

Table *46*.

Table 46 Descriptive statistics for actual value at baseline and change from baseline of SF-36 subscales and components summaries (ITT set and ITT-treatment period II subset)

Physical Component Score			
Visit, Statistics	**CT-P47 (N=234)**	**EU-RoActemra (N=237)**	
	Change from baseline		
Baseline [a]			
Mean (SD)	34.735 (5.6581)	35.077 (5.8052)	
Week 12			
Mean (SD)	6.335 (6.1896)	6.319 (6.5910)	
Week 24			
Mean (SD)	8.048 (7.2097)	7.813 (7.2057)	
Visit, Statistics	**CT-P47 Maintenance (N=225)**	**EU-RoActemra Maintenance (N=109)**	**Switched to CT-P47 (N=110)**
Week 24			
Mean (SD)	8.052 (7.2258)	7.764 (7.2608)	8.148 (7.0656)
Week 32			
Mean (SD)	8.235 (7.2751)	8.470 (7.6246)	8.709 (6.6612)
Week 52			
Mean (SD)	9.030 (9.6025)	10.084 (8.9579)	10.216 (8.7914)
Mental Component Score			
Visit, Statistics	**CT-P47 (N=234)**	**EU-RoActemra (N=237)**	
	Change from baseline		
Baseline [a]			
Mean (SD)	38.546 (9.1298)	39.090 (10.2027)	
Week 12			
Mean (SD)	4.614 (8.4209)	5.685 (8.5755)	
Week 24			
Mean (SD)	5.642 (9.4119)	7.150 (9.5005)	
Visit, Statistics	**CT-P47 Maintenance (N=225)**	**EU-RoActemra Maintenance (N=109)**	**Switched to CT-P47 (N=110)**
Week 24			
Mean (SD)	5.673 (9.4217)	7.697 (9.2842)	6.527 (9.1092)
Week 32			
Mean (SD)	6.082 (9.2211)	7.477 (8.7876)	7.550 (10.1349)
Week 52			
Mean (SD)	6.993 (9.8512)	8.326 (8.8794)	9.038 (10.0177)

Abbreviations: ITT, intent-to-treat; SD, standard deviation; SF-36, Medical Outcomes Study Short-Form Health Survey

[a] For the baseline value, actual results were presented.

Joint Surgery

During TP I, one (0.4%) patient in the CT-P47 group and 2 (0.8%) patients in the RoActemra group had joint surgery. During TP II, one (0.4%) patient in the CT-P47 maintenance group, 3 (2.8%) patients in the RoActemra maintenance group, and 1 (0.9%) patient in the switched to CT-P47 group had joint surgery. Some patients had multiple joint surgery events. Reasons for joint surgery included hip arthroplasty, arthrodesis, bunion operation, toe amputation, open reduction of fracture, arthroscopy, joint irrigation, synovectomy, knee arthroplasty, hip surgery due to TESAE of femoral neck fracture, and fracture treatment with consequent joint stabilisation.

The patients who received joint surgery were generally similar among the treatment groups with small numbers. There were no patients who received joint surgery before Week 12 without study drug discontinuation, so no patients were excluded from PPS.

Radiological progression

Joint damage progression based on radiographic evaluations was assessed by the change in the total Sharp score using the modified total Sharp scoring system. Actual values and change from baseline in total sharp scores are presented in **Table 47.**

Table 47 Mean (SD) for *actual value and change from baseline of total sharp scores*: ITT set.

Visit Statistic	CT-P47 Maintenance (N=225)	RoActemra Maintenance (N=109)	Switched to CT-P47 (N=110)
	Change from baseline		
Baseline [a] Mean (SD)	31.19 (47.022)	36.10 (56.185)	35.66 (47.099)
Week 52 (EOS) [b] Mean (SD)	0.57 (2.449)	0.09 (1.166)	0.46 (2.137)

Abbreviations: EOS, end-of-study; ITT, intent-to-treat; SD, standard deviation.
Note. Joint damage progression based on radiographic evaluations was assessed by the change in the total Sharp score using the modified total Sharp scoring system.
[a] For the baseline value, actual results were presented
[b] For Week 52 (EOS) value, change from baseline results were presented

- **Ancillary analyses**

There were no predefined subgroup analyses. Nevertheless, the applicant conducted post-hoc analyses on Treatment Period I results based on based on age, sex, ethnicity, and body weight at Day 1 in demographic subgroup and DAS28 (ESR) score at screening and prior biologic use approved for RA in disease factor subgroup. In the post-hoc subgroup analyses, efficacy was mostly comparable between study groups. However, in two very small subgroups, efficacy of CT-P47 appeared to be lower than that of RoActemra: in subjects with low DAS28(ESR) value at baseline (≤5.1) (n=5 in the CTP-47 group and 6 in the RoActemra group), and in the subgroup of Hispanic or Latino subjects (6 in the CT-P47 group and 4 in the RoActemra group). Taking in account the small number of subjects in the discrepant subgroups and the very wide confidence intervals in these subgroups, no conclusion can be drawn from these post-hoc analyses.

Since there was only one Phase 3 study, no pooled analyses have been performed. The applicant however provided a comparison of efficacy between study CT-P47 and key tocilizumab studies with similar design in RA Patients, showing consistent results of study CT-P47 3.1 with the historical Actemra/RoActemra studies.

Close to half of patients in each group reported use of systemic corticosteroids (45.7% and 47.3% in the CT-P47 and RoActemra groups, respectively). Anti-inflammatory and antirheumatic products were used by 39.3% and 44.7% of patients in the CT-P47 and RoActemra groups, respectively. During Treatment Period II up to EOS, 48.0%, 49.5% and 45.5% of patients had taken at least one concomitant medication in the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups, respectively. The most frequent concomitant medication by drug class during Treatment Period II was antibacterials for systemic use (19.6%, 20.2% and 13.6% of patients in the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups, respectively), followed by analgesics (7.6%, 8.3% and 12.7% of patients in the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups, respectively). Hence, the use of concomitant medication was overall similar across study groups.

From Week 16 and thereafter, patients who had less than a 20% improvement in both swollen and tender joint counts compared to baseline could have received rescue treatment at the discretion of the investigator. Few patients met this criterion. Ultimately, no patients received rescue therapy by the investigator's decision.

- **Summary of main efficacy results**

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

Table 48 Summary of efficacy for trial CT-P47 3.1

Title: A Randomized, Active-Controlled, Double-Blind, Phase 3 Study to Compare Efficacy and Safety of Two Intravenous Infusion Formulations of Tocilizumab (CT-P47 and RoActemra) when Co-administered with Methotrexate in Patients with Moderate to Severe Active Rheumatoid Arthritis		
Study identifier	Protocol number: CT-P47 3.1 EudraCT Number:2022-001066-36	
Design	This study was a randomised, active-controlled, double-blind, multicentre, Phase 3 study designed to evaluate efficacy, PK, and overall safety including immunogenicity of multiple dose (8 mg/kg, not exceeding 800 mg/dose) of either CT-P47 or RoActemra administered by intravenous (IV) every 4 weeks (Q4W) in combination with Methotrexate (MTX) (between 10 to 25 mg/week, oral or parenteral; intramuscular [IM] or subcutaneous(ly) [SC] dose) and folic acid (≥5 mg/week, oral dose). The MTX dose and route were maintained from the beginning to the end of the study. Target group: female and male patients (aged 18 to 75 years) with moderate to severe active rheumatoid arthritis.	
	Duration of screening period: Duration of Treatment Period II: Treatment Period II: End of study visit	6 weeks 28 weeks Week 24 to Week 52 Week 52
Hypothesis	Equivalence	

Title: A Randomized, Active-Controlled, Double-Blind, Phase 3 Study to Compare Efficacy and Safety of Two Intravenous Infusion Formulations of Tocilizumab (CT-P47 and RoActemra) when Co-administered with Methotrexate in Patients with Moderate to Severe Active Rheumatoid Arthritis			
Study identifier	Protocol number: CT-P47 3.1 EudraCT Number:2022-001066-36		
Treatments groups Treatment Period I	Treatment Period I CT-P47 (TP1 CT-P47)		CT-P47 8 mg/kg by IV infusion Q4W
	Treatment Period I EU-RoActemra (TP1 CT-P47)		EU-RoActemra 8 mg/kg by IV infusion Q4W
Treatments groups Treatment Period II	Treatment Period II CT-P47 (TP2 CT-P47)		CT-P47 8 mg/kg by IV infusion Q4W
	Treatment Period II EU-RoActemra (TP2 RoActemra)		EU-RoActemra 8 mg/kg by IV infusion Q4W
	EU-RoActemra in TP1 switched to CT-P47 in TP2 (TP2 Switch)		CT-P47 8 mg/kg by IV infusion Q4W
Endpoints and definitions	Primary endpoint	DAS28(ESR) CFB Week 12	Change from baseline (CFB) in DAS28 (ESR) at Week 12. DAS28(ESR) is a score calculated based on erythrocyte sedimentation rate (ESR), Tender Joint Count (0-28), SJC28 = Swollen Joint Count (0-28), and patient's global disease activity measured on VAS (0-100 mm).
	Secondary endpoint	DAS28(ESR) CFB Week 52	Change from baseline (CFB) in DAS28 (ESR) at Week 52
	Secondary endpoint	ACR20/50/70 at Week 12	American College of Rheumatology definition of a 20%/50%/70% improvement criteria
	There were no key secondary endpoints. All secondary endpoints were analysed descriptively. DAS28 (ESR) at week 52 and ACR20/50/70 at Week 12 are given here as an example secondary endpoints. All secondary endpoints gave comparable results across the three treatment groups during Treatment Periods I and II in both ITT and Per Protocol analyses.		
Database lock	23 Nov 2023 (last patient Week 52 visit)		
Results and Analysis			
Analysis description	**Primary Analysis** of the primary endpoint: DAS28-ESR Change from baseline at Week 12		

Title: A Randomized, Active-Controlled, Double-Blind, Phase 3 Study to Compare Efficacy and Safety of Two Intravenous Infusion Formulations of Tocilizumab (CT-P47 and RoActemra) when Co-administered with Methotrexate in Patients with Moderate to Severe Active Rheumatoid Arthritis			
Study identifier	Protocol number: CT-P47 3.1 EudraCT Number:2022-001066-36		
Analysis population and time point description	Intent to Treat Analysis Set: includes all randomised patients Male or female patients with moderate to severe active RA Week 12		
Descriptive statistics and estimate variability	Treatment group	TP1 CT-P47	TP1 EU-RoActemra
	Number of subjects	221	225
	DAS28-ESR Change from baseline to week 12 (LS Mean)	-3.01	-3.00
	Standard Error (SE)	0.121	0.120
Effect estimate per comparison	Primary endpoint	Comparison groups	CT-P47 and EU-RoActemra
		Estimate of Treatment Difference	-0.01
		Confidence interval of Treatment Difference	(-0.26, 0.24)
		P-value	N/A
Analysis description	**Supportive Analysis of the primary endpoint**: DAS28-ESR Change from baseline at Week 12		
Analysis population and time point description	Per Protocol Analysis Set (PPS): includes all randomised patients compliant with therapy (≥80% of planned cumulative doses up to Week 8) and have a DAS28 (ESR) assessment at baseline and Week 12 and do not have any major protocol deviation affecting primary efficacy endpoint Male or female patients with moderate to severe active RA Week 12		
Descriptive statistics and estimate variability	Treatment group	TP1 CT-P47 (PPS)	TP1 EU-RoActemra (PPS)
	Number of subjects	213	207
	DAS28-ESR Change from baseline to week 12 (LS Mean)	-3.05	-3.09
	Standard Error (SE)	0.121	0.119
	Primary endpoint	Comparison groups	CT-P47 (PPS) and EU-RoActemra (PPS)

Title: A Randomized, Active-Controlled, Double-Blind, Phase 3 Study to Compare Efficacy and Safety of Two Intravenous Infusion Formulations of Tocilizumab (CT-P47 and RoActemra) when Co-administered with Methotrexate in Patients with Moderate to Severe Active Rheumatoid Arthritis				
Study identifier	Protocol number: CT-P47 3.1 EudraCT Number:2022-001066-36			
		Estimate of Treatment Difference	0.04	
		Confidence interval of Treatment Difference	(-0.20, 0.29)	
		P-value	N/A	
Analysis description	**Secondary Analysis of the secondary endpoint:** DAS28-ESR Change from baseline at Week 52			
Descriptive statistics and estimate variability	Treatment group	TP2 CT-P47 (ITT)	TP2 EU-RoActemra (ITT)	TP2 Switch (ITT)
	Number of subjects	225	109	110
	DAS28-ESR Change from baseline to week 52 (Mean)	-4.279	-4.231	-4.376
	Standard Deviation (SD)	1.1934	1.3046	1.4212
Analysis description	**Secondary Analysis of the secondary endpoint:** Proportion of Patients achieving Response according to ACR20/50/70 at Week 24			
Descriptive statistics	Treatment group	TP1 CT-P47 (ITT)	TP1 EU-RoActemra (ITT)	
	Number of subjects	234	237	
	ACR20	199 (85)	189 (79.7)	
	ACR50	142 (60.7)	146 (61.6)	
	ACR70	100 (42.7)	99 (41.8)	

2.6.5.3. Clinical studies in special populations

Not applicable for biosimilars.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Not applicable.

2.6.5.6. Supportive study(ies)

Usability of the PFS and AI

One usability study (CT-P47 3.2) has been conducted. The study was a single-arm, open-label, multiple-dose, phase 3 study designed to evaluate usability of CT-P47 (162 mg/0.9 mL) autoinjector (AI) in patients with moderate to severe active rheumatoid arthritis (RA).

The primary objective of study was to evaluate usability of Auto-injector (AI) assessed by patient (POST-self-injection assessment questionnaire [SIAQ]) at week 2.

The secondary usability endpoints were the usability of AI as assessed by patients rating using PRE- and POST-SIAQ at week 0, the usability of AI as assessed by patients rating using PRE-SIAQ at week 2 and the observer rating of successful self-injection of AI using self-injection assessment checklist at weeks 0 and 2. The study drug of CT-P47 was administered by SC injection via AI at Week 0 and Week 2 and then via pre-filled syringe (PFS) until week 10. The usability screening period was weeks 0-2. Thus, the usability study only covers the usability of the autoinjector and not the pre-filled syringe. Upon request, the applicant also provided data on the usability of the pre-filled syringe during the procedure.

In the usability study, for self-injection of study drug, the investigator or designated study centre staff instructed the patients on the proper use of each device before self-injection of CT-P47 AI. Patients self-injected the study drug at the study centre under the investigator or designated study centre staff's supervision. Printed instructions for use (IFU) of AI and instructions for self-injection of study drug were provided to the patients. A total of 32 patients were analysed in the usability set. The mean scores on all domains of the SIAQ at Weeks 0 and 2 in the Usability and Safety Sets were over 6 for pre- and post-injection. The mean scores on all domains of the POST-SIAQ at Week 2 in the Usability Set was over 8, except for the domain of self-confidence (7.11) and satisfaction with self-injection (7.98). All patients were able to complete successfully all 14 instructions from the self-injection assessment checklist at weeks 0 and 2. The IFU contains step by step instructions on how to inject with the tocilizumab autoinjector and tocilizumab PSF+NSD along with graphic representations of what each step looks like.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The submission contains the CSR for the Phase 3 study CT-P47 3.1, conducted in patients with moderately to severely active rheumatoid arthritis (RA) in multiple study sites in Poland. Study CT-P47 3.1 is a randomised, active-controlled, double-blind, multicentre, Phase 3 study designed to evaluate efficacy, PK, and overall safety including immunogenicity of multiple dose (8 mg/kg, not exceeding 800 mg/dose) of either CT-P47 or EU-RoActemra administered intravenously (IV) every 4 Weeks (Q4W) in combination with Methotrexate (MTX) (between 10 to 25 mg/Week, oral or parenteral; intramuscular [IM] or Subcutaneous [SC] dose) and folic acid (≥5 mg/Week, oral dose). The MTX dose and route were maintained from the beginning to the end of the study. Overall, the study plan is appropriate and in line with scientific advice from the CHMP.

The duration of the study was up to 52 Weeks, which includes Screening (6 Weeks), Treatment Period I (24 Weeks), and Treatment Period II (from week 24 to prior to Week 52 end of study visit). Patients

were initially randomised to CT-P47 or EU-RoActemra at baseline for Treatment Period I. Prior to dosing at Week 24, all patients underwent the second randomisation process. Patients from the EU-RoActemra group were randomised again in a ratio of 1:1 to either continue with EU-RoActemra or undergo transition to CT-P47, whereas patients originally randomised to CT-P47 continued using it during Treatment Period II. All patients received assigned study drug Q4W from Week 24 and thereafter up to Week 48 (last administration of study drug). The study design and treatment periods are deemed adequate. Methodology is adequate, including randomisation and blinding methods.

The patients were required to be aged 18-75 years, both inclusive, to have had a diagnosis of RA according to the 2010 ACR/EULAR classification criteria for at least 24 weeks prior to the first administration of the study drug and required to have been receiving oral or parenteral MTX for at least 12 weeks and been on a stable dose and route of MTX between 10 to 25 mg/week for at least 8 weeks prior to the first administration of the study drug, combined with folate treatment. Patients were required to have had inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). A patient with 1 prior biologic agent for the treatment of RA could be enrolled after sufficient wash-out period. Patients were excluded if they had previously received investigational or licensed product; more than 1 biologic agents approved for the treatment of RA; targeted synthetic DMARD(s) (e.g., tofacitinib, baricitinib) for the treatment of RA and/or rituximab and/or an IL-6 inhibitor for any purposes. The target population and inclusion/exclusion criteria are considered appropriate.

The stratification factors for the first randomisation were body weight (<100 kg or ≥100kg) measured on Day 1, disease activity by DAS28 (ESR) score at Screening (>5.1 or ≤5.1) and prior biologic use approved for RA treatment (yes or no). The stratification factor for the second randomisation for the ITT-Treatment Period II subset was disease activity by DAS28 (ESR) score at Week 20 (<2.6 vs.≥2.6). The stratification factors are acceptable.

The primary endpoint was mean change from baseline of DAS28 (ESR) at Week 12. DAS28 (ESR) is a well-established and validated measure of disease activity in RA and as such acceptable. DAS28 (ESR) is a continuous score based on the following individual components: tender/swollen joint counts out of 28 joints [DAS28 assessment], VAS scores for patient's global assessment of disease activity, and erythrocyte sedimentation rate (ESR). The secondary efficacy endpoints included American College of Rheumatology definition of a 20%/50%/70% improvement criteria (ACR20, ACR50 and ACR70), individual components of the ACR, hybrid ACR response, DAS 28 (CRP/ESR), individual components of DAS28, European League against Rheumatism (EULAR) response, simplified disease activity index (SDAI), clinical disease activity index (CDAI), ACR/EULAR remission (Boolean-based definition), Health-Related Quality of Life (SF-36), and joint damage progression based on radiographic evaluations (1 image of both the right and left hands and both the right and left feet, for a total of 4 images.) Joint damage progression was assessed at 52 weeks by the change in the total Sharp score using the modified total Sharp scoring system at each scheduled visit. All endpoints are validated and customary measures of disease activity in RA studies and as such acceptable. Secondary endpoints were not powered for equivalence and no multiplicity control was included. Hence, the results on secondary endpoints are reported descriptively, which is appropriate.

The choice of the therapeutic indication, the clinical setting, the primary endpoint and secondary endpoints are in line with the CHMP guidance and were endorsed in CHMP Scientific Advice. The prespecified equivalence margin of the primary efficacy estimand DAS28(ESR) at Week 12 set to [−0.6, 0.6] is also endorsed. The clinical model is considered sufficiently sensitive to enable the detection of differences between the two products.

Statistical methods

Advice was given by the CHMP in 2021 (EMA/SA/0000050398) regarding the primary endpoint, sample size calculations, estimands, handling of missing data and statistical analyses. Those advice were largely followed.

The difference of mean change from baseline of DAS28 (ESR) score at Week 12 was analysed using an ANCOVA model with treatment as a fixed effect and randomisation stratification variables as covariates. This is conventional and thus endorsed.

The assumptions for the sample size in CT-P47 Study 3.1 are reasonable and in line with the recommendation from CHMP SAWP. The assessment of clinical equivalence was based on a 95% CI. The prespecified equivalence margin of the primary efficacy endpoint (DAS28 (ESR) at Week 12) was set to ±0.6. This is endorsed.

No adjustment for multiplicity was needed as there was only one primary endpoint and all secondary endpoints were analysed descriptively.

The changes from protocol-specified analyses, i.e. increasing the number of MI iterations from 10 to 100 and using the continuous value baseline DAS28 (ESR) score as covariate instead of the dichotomous stratification factor (>5.1 or ≤ 5.1), are acceptable.

Efficacy data and additional analyses

Overall, 471 male (n=110) and female (n=361) patients with RA were enrolled in a 1:1 ratio into the CT-P47 (N=234) or EU-RoActemra (N=237) groups. Age range of study subjects was 20 to 73 years. A great majority of all participants had RA with severe disease activity as defined by DAS28(ESR) ≥5.1 at baseline (n=433; 97.5%). In line with prevalence of RA in general population, one fourth of study subjects were male (n=110) and the majority were female (n=361). Also other baseline characteristics and distribution of stratification factors were comparable in the CT-P47 or EU-RoActemra randomised for Treatment Period I and across the three study group during Treatment Period II.

The primary efficacy endpoint, mean change from baseline of DAS28 (ESR) at Week 12, has met the predefined criteria with the 95% CI of comparison between groups falling within the pre-specified margin of (-0.6, 0.6) in both ITT and PP Sets: 95% CI: [-0.26, 0.24] in the ITT Set and 95% CI: [-0.20, 0.29] in PP set. The primary endpoint DAS28 (ESR) is a validated and conventional measure of treatment response in RA and a continuous variable, thus more sensitive for detecting differences between products than categorical measures such as the ACR20/50/70 responses.

Comparable results were observed in the descriptive analysis of all secondary endpoints between the CT-P47 and EU-RoActemra groups during the study. The mean actual values and change from baseline of DAS28 (ESR) and DAS28 (CRP) were similar between study groups. The proportion of patients achieving clinical response according to the ACR20, ACR50, and ACR70 criteria was similar between the 2 groups in Treatment Period I and the three groups in Treatment Period II. Sustained efficacy to comparable extent was achieved also in other secondary efficacy endpoints in the Switched to CT-P47 group as well as the CT-P47 and EU-RoActemra maintenance groups during Treatment Period II up to Week 52 (end of study). The mean increase from baseline in total sharp radiographic joint damage scores was at week 52 generally similar among the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups in the ITT maintenance set. At end of the study (Week 52), around 1/3 of subjects had achieved ACR/EULAR remission (Boolean-based definition): 32.4%, 32.1% and 37.3% in the CT-P47, RoActemra Maintenance and Switched to CT-P47 groups, respectively.

A total of 120 (25.5%) patients, 24.8% and 26.2% in the CT-P47 and RoActemra groups, respectively, had used 1 prior biologic approved for RA treatment before the first administration of the study drug.

Even though only a small proportion of subjects had moderately active RA, the patients can be regarded to sufficiently represent the target population of tocilizumab treatment.

All patients were treated with concomitant methotrexate and folate. Methotrexate use could potentially impact on the extrapolation to indications where tocilizumab is intended for monotherapy, since concomitant methotrexate is expected to decrease the risk for immunogenicity. However, taking in account the overall low immunogenicity of tocilizumab, this issue is not considered to prevent extrapolation to other indications for use.

Discontinuations from study drug were relatively infrequent, since 96.2% and 92.4% of subjects in the CT-P47 and RoActemra groups completed Treatment Period I, respectively. All subjects who were re-randomised to Treatment Period II initiated the period, and a great majority completed treatment up to Week 52 (EOS): 210 (93.3%), 100 (91.7%) and 102 (92.7%) subjects of the CT-P47 Maintenance, RoActemra Maintenance and Switched to CT-P47 groups, respectively. Discontinuations from study drug were distributed relatively evenly during TP 2 across study groups and are not deemed to affect the validity of the results.

The use of concomitant medication was overall similar across study groups.

The mode of action of tocilizumab is similar across approved indications of RoActemra. Tocilizumab binds to soluble and membrane bound IL-6 receptors, blocking IL-6 from exerting its pro-inflammatory effects. Extrapolation to all indications of RoActemra is considered possible based on the clinical study conducted in patients with rheumatoid arthritis.

One usability study (CT-P47 3.2) has been conducted to evaluate usability of Auto-injector (AI). The usability study included patients aged 27 years and older. However, the sought therapeutic indications for the product include use in children and adolescents (i.e. under 18 years of age) from the age of 1 year (prefilled syringe) and from 2 years (infusion concentrate) and from 12 years (prefilled pen). The subjects could be included, e.g., from the age of 10 onwards, since younger children are likely to be helped by their caregivers, but older paediatric patients often administer the medication themselves. Additionally, many patients with active rheumatoid arthritis, systemic juvenile idiopathic arthritis and juvenile idiopathic polyarthritis have decreased ability to handle devices due to diminished muscle power in the hands and wrists and often multiple active, tender and swollen joints in fingers, hands and wrists. Therefore, usability of the devices is especially important to have been justified in these vulnerable patient groups. The applicant was requested to provide data on the usability of the autoinjector and pre-filled syringe in patients under 18 years of age during the procedure. As a response to the request, the applicant submitted results of the human factor (HF) validation study which included also paediatric patients. The HF validation study provided adequate evidence that the autoinjector is safe and effective for the intended users, uses, and use environments when used according to the IFU.

2.6.7. Conclusions on the clinical efficacy

The pivotal study CT-P47 3.1 included 471 adult subjects with moderate to severe RA randomised 1:1 to either CT-P47 or EU-RoActemra for a 24-week Treatment Period I followed by a Treatment Period II from Week 24 up to end-of-study visit at Week 52. The data indicate therapeutic equivalence in efficacy between CT-P47 and EU-RoActemra in this sensitive clinical model of RA and therefore, supports biosimilarity with respect to efficacy.

2.6.8. Clinical safety

The safety assessment in the clinical studies conducted with CT-P47 took into account the known safety profile of EU-RoActemra/US-Actemra. Safety assessments for the clinical studies include monitoring and recording of adverse events (AEs) (including treatment-emergent adverse events [TEAEs] and treatment emergent serious adverse events [TESAEs]), AEs of special interest (AESIs), local injection site pain (only in Studies CT-P47 1.1 and CT-P47 1.3), immunogenicity, hypersensitivity monitoring (via monitoring of vital signs) and vital signs monitoring (including systolic and diastolic BP, heart rate, respiratory rate and body temperature), weight measurement, electrocardiograms (ECGs) including hypersensitivity monitoring, physical examination findings, interferon γ release assay (IGRA), chest X-ray (optional in Studies CT-P47 1.1, CT-P47 1.2 and CT-P47 1.3), hepatitis B and hepatitis C and human immunodeficiency virus (HIV) status, pregnancy tests, clinical laboratory testing (including clinical chemistry, haematology, viral serology, urinalysis and others), clinical signs and symptoms of tuberculosis (TB) and prior and concomitant medications.

An AESI was defined as an event of infection, hypersensitivity reactions including anaphylaxis, hepatic event, haemorrhage (medically significant bleeding events), gastrointestinal perforation, malignancy and demyelinating disorder for all studies. Injection site reactions were considered an AESI only for SC Studies CT-P47 3.2, CT-P47 1.1 and CT-P47 1.3. The following queries were used for AESI analyses:

- Infection
    - AEs coded with a SOC of 'Infections an Infestations'
- Hypersensitivity, including anaphylaxis
    - TEAEs checked as Hypersensitivity/anaphylaxis in the eCRF. Anaphylaxis will be reviewed medically according to Sampson criteria (Sampson et al., 2006).
- Hepatic event
    - MedDRA SMQ Hepatic disorder (narrow)
- Haemorrhage (medically significant bleeding events)
    - Standardised MedDRA Query (SMQ) Haemorrhage terms (narrow) (excluding laboratory terms)
- Gastrointestinal perforation
    - SMQ GI perforation (narrow) followed by medical review
- Malignancy
    - SMQ Malignant or unspecified tumours (narrow)
- Demyelinating disorder
    - SMQ Demyelination (narrow)

Safety results are separately presented for data from Studies CT P47 3.1 and CT-P47 3.2 (in patients with moderate to severe active RA) and the healthy volunteer studies CT-P47 1.1, CT-P47 1.2 and CT P47 1.3. All safety analyses were conducted using the Safety Set, which is defined as all randomly assigned subjects who receive at least 1 dose (full or partial) of study drug (CT-P47 or EU-RoActemra or US-Actemra). In Study CT-P47 3.1, the Safety-Treatment Period II subset consists of all patients in Safety Set who received at least 1 dose (full or partial) of study drug (CT-P47 or EU RoActemra) at or after Week 24. Subjects/patients were assigned to a treatment group based on the study drug they actually received.

In Study CT-P47 3.1, the study period contains Screening Period (Day -42 to Day -1), Treatment Period I (from Week 0 [Day 1] to Week 24 pre-dose), Treatment Period II (from Week 24 to prior to Week 52; includes switched group) and EOS visit (Week 52) based on the visit. Treatment emergent adverse events (TEAEs) with an actual/imputed start date prior to the first administration of study drug in Treatment Period II, or TEAEs for those patients who did not administer study drug during Treatment Period II were included in Treatment Period I (from Week 0 up to Week 24 pre-dose).

Treatment emergent adverse events (TEAEs) with an actual/imputed start date on or after the date of first administration of study drug in Treatment Period II were included in Treatment Period II.

Safety results of Study CT-P47 3.1 are separately summarised for Treatment Period I, Treatment Period II and Overall Period up to Week 52. For the Overall Period, the AEs up to Week 52 are also presented based on a) the actual treatment groups for Treatment Period I (CT-P47 and EU-RoActemra groups), and b) the actual treatment groups for Treatment Period II (CT-P47 maintenance, EU-RoActemra maintenance and Switched to CT-P47 groups).

For AE coding, the Medical Dictionary for Regulatory Activities (MedDRA) ver. 25.0 was used in Studies CT-P47 1.1 and CT-P47 1.2, ver. 25.1 in Study CT-P47 1.3 and ver. 26.0 in Studies CT-P47 3.1 and CT-P47 3.2. Intensity of AEs was assessed based on Common Terminology Criteria for Adverse Events (CTCAE) ver. 5.0 in all studies. The causality or association to study drug in causing or contributing to the AE was classified into the categories "unrelated", "possible", "probable", and "definite". AEs classified as "possible", "probable" or "definite" were considered "related" and combined for analysis of related events.

2.6.8.1. Patient exposure

Table 49 Number of subjects who received at least 1 dose of study drug (CT-P47, EU-RoActemra or US-Actemra) in CT-P47 studies (safety set)

Study (RoA)	Subjects	Duration of Exposure	Number of Subjects				
			CT-P47 only	EU-RoActemra only	EU-RoActemra /CT-P47	US-Actemra only	Total
CT-P47 3.1 (IV)	Moderate to severe active RA	At least 1 dose	234	127	110[1]	-	471
		Continued on Study Drug up to Week 32 treatment [2]	222	107	107[1]	-	436
		Continued on Study Drug up to Week 48 treatment [3]	211	100	102	-	413
CT-P47 3.2 (SC)	Moderate to severe active RA	At least 1 dose	33	-	-	-	33
		up to Week 10 treatment	29[3]	-	-	-	29
CT-P47 1.1 (SC)	Healthy subjects	Single dose	158	155	-	-	313
CT-P47 1.2 (IV)	Healthy subjects	Single dose	45	43	-	44	132
CT-P47 1.3 (SC)	Healthy subjects	Single dose	310	-	-	-	310
Total		**At least 1 dose**	**780**	**325**	**217**	**44**	**1,259**

Study (RoA)	Subjects	Duration of Exposure	Number of Subjects				
			CT-P47 only	EU-RoActemra only	EU-RoActemra /CT-P47	US-Actemra only	Total

[1] Patients who were initially randomised to EU-RoActemra were randomised again in a ratio of 1:1 to either continue with EU-RoActemra or undergo transition to CT-P47 from Week 24
[2] Regardless of the actual dose administration, the number of patients who remained until Week 32 treatment without discontinuing the study was included
[3] Regardless of the actual dose administration, the number of patients who remained until Week 48 treatment without discontinuing the study was included
Abbreviation: RoA, route of administration

2.6.8.2. Adverse events

Adverse events in studies in RA patients

Study CT-P47 3.1

An overall summary of TEAEs from Study CT-P47 3.1 in RA patients in the Overall Period, i.e. Treatment Period I (TP I) and Treatment Period II (TP II), is provided in **Table 50**. In total, 1791 TEAEs were reported in 415/471 (88.1%) patients and the proportion of patients was similar between the CT-P47 and RoActemra groups (205/234 [87.6%] and 210/237 [88.6%] patients, respectively), and among the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups (197/225 [87.6%], 96/109 [88.1%], and 96/110 [87.3%] patients, respectively).

The majority of TEAEs were grade 2 or 3 in intensity. Treatment-emergent AEs considered by the investigator to be related to the study drug were reported in 295/471 (62.6%) patients, and the proportion of patients was similar between CT-P47 and RoActemra groups (141/234 [60.3%] and 154/237 [65.0%] patients, respectively), and among the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups (136/225 [60.4%], 70/109 [64.2%], and 69/110 [62.7%] patients, respectively).

Table 50 Summary of treatment-emergent adverse events (overall period): safety set.

	Initial Randomization		2nd Randomization		
	CT-P47 (N=234)	RoActemra (N=237)	CT-P47 Maintenance (N=225)	RoActemra Maintenance (N=109)	Switched to CT-P47 (N=110)
Total number of TEAEs	**898**	**893**	**877**	**411**	**418**
Number (%) of patients with at least 1 TEAE	205 (87.6)	210 (88.6)	197 (87.6)	96 (88.1)	96 (87.3)
Related to the study drug	141 (60.3)	154 (65.0)	136 (60.4)	70 (64.2)	69 (62.7)
Unrelated to the study drug	162 (69.2)	171 (72.2)	154 (68.9)	78 (71.6)	77 (70.0)
Total number of TESAEs	**23**	**29**	**22**	**10**	**15**
Number (%) of patients with at least 1 TESAE	20 (8.5)	23 (9.7)	19 (8.4)	9 (8.3)	11 (10)
Related to the study drug	4 (1.7)	4 (1.7)	4 (1.8)	1 (0.9)	3 (2.7)
Unrelated to the study drug	16 (6.8)	19 (8.0)	15 (6.7)	8 (7.3)	8 (7.3)
Total number of TEAEs leading to study drug discontinuation	**13**	**22**	**10**	**5**	**4**
Number (%) of patients with at least 1 TEAE leading to study drug discontinuation	13 (5.6)	20 (8.4)	10 (4.4)	5 (4.6)	4 (3.6)
Related to the study drug	8 (3.4)	16 (6.8)	5 (2.2)	3 (2.8)	4 (3.6)
Unrelated to the study drug	5 (2.1)	4 (1.7)	5 (2.2)	2 (1.8)	0
Total number of TEAEs classified as Infection	**243**	**203**	**238**	**95**	**97**
Number (%) of patients with at least 1 TEAE classified as infection	131 (56.0)	117 (49.4)	127 (56.4)	52 (47.7)	55 (50.0)
Total number of TEAEs classified as Hypersensitivity reactions	**6**	**8**	**6**	**1**	**1**
Number (%) of patients with at least 1 TEAE classified as hypersensitivity reactions	4 (1.7)	7 (3.0) [b]	4 (1.8)	1 (0.9)	1 (0.9)
Total number of TEAEs classified as Hepatic Event	**163**	**185**	**159**	**84**	**90**
Number (%) of patients with at least 1 TEAE classified as hepatic event	81 (34.6)	94 (39.7)	78 (34.7)	41 (37.6)	44 (40.0)
Total number of TEAEs classified as Hemorrhage [c]	**5**	**11**	**5**	**4**	**7**
Number (%) of patients with at least 1 TEAE classified as hemorrhage	4 (1.7)	9 (3.8)	4 (1.8)	4 (3.7)	5 (4.5)

Total number of TEAEs classified as Gastrointestinal Perforation	**2**	**0**	**2**	**0**	**0**
Number (%) of patients with at least 1 TEAE classified as gastrointestinal perforation	2 (0.9)	0	2 (0.9)	0	0
Total number of TEAEs classified as malignancy	**0**	**1**	**0**	**0**	**0**
Number (%) of patients with at least 1 TEAE classified as malignancy	0	1 (0.4)	0	0	0
Total number of TEAEs classified as Demyelinating Disorder	**0**	**0**	**0**	**0**	**0**
Total number of TEAEs leading to Death	**1**	**0**	**1**	**0**	**0**
Number (%) of patients with at least 1 TEAE leading to death	1 (0.4) [a]	0	1 (0.4) [a]	0	0

Abbreviations: TEAE, treatment-emergent adverse event; TEAESI, treatment-emergent adverse event of special interest; TESAE, treatment-emergent serious adverse event.
Note: The total number of TEAEs count included all patient events. At each level of summarisation, a patient was counted once if they reported 1 or more events. The event was considered to be related if the relationship was defined as 'possible', 'probable' or 'definite'.
[a] In 1 patient, peritonitis was occurred after gastroscopy for medical work-up. This case was classified as TESAE, TEAESI of infection, TEAESI of gastrointestinal perforation, and death.
[b] One case was classified as anaphylaxis.
[c] All events were considered as non-medically significant bleeding events except for 1 grade 3 TEAE of uterine haemorrhage reported in the switched to CT-P47 group.

A summary of all TEAEs by SOC and PT reported for 5% or more patients in any treatment group in Study CT-P47 3.1 is displayed in **Table 51.**

Table 51 Treatment-emergent adverse events reported for ≥5% of patients in any treatment group using preferred term (overall period): safety set.

	Initial Randomization		2nd Randomization		
	CT-P47 (N=234)	RoActemra (N=237)	CT-P47 Maintenance (N=225)	RoActemra Maintenance (N=109)	Switched to CT-P47 (N=110)
Preferred Term	Number (%) of patients				
Alanine aminotransferase increased	51 (21.8)	64 (27.0)	49 (21.8)	29 (26.6)	30 (27.3)
Upper respiratory tract infection	61 (26.1)	52 (21.9)	60 (26.7)	28 (25.7)	22 (20.0)
Leukopenia	28 (12.0)	33 (13.9)	28 (12.4)	13 (11.9)	17 (15.5)
Neutropenia	26 (11.1)	34 (14.3)	24 (10.7)	13 (11.9)	19 (17.3)
Nasopharyngitis	25 (10.7)	25 (10.5)	24 (10.7)	11 (10.1)	13 (11.8)
Aspartate aminotransferase increased	21 (9.0)	28 (11.8)	21 (9.3)	13 (11.9)	13 (11.8)
Hypercholesterolaemia	20 (8.5)	21 (8.9)	20 (8.9)	12 (11.0)	9 (8.2)
Blood creatine phosphokinase MB increased	14 (6.0)	16 (6.8)	14 (6.2)	11 (10.1)	5 (4.5)
Hypertension	10 (4.3)	18 (7.6)	10 (4.4)	11 (10.1)	7 (6.4)
Lymphopenia	12 (5.1)	15 (6.3)	12 (5.3)	8 (7.3)	4 (3.6)
Latent tuberculosis	16 (6.8)	8 (3.4)	16 (7.1)	3 (2.8)	5 (4.5)
Pharyngitis	13 (5.6)	11 (4.6)	13 (5.8)	5 (4.6)	6 (5.5)
Transaminases increased	10 (4.3)	14 (5.9)	9 (4.0)	3 (2.8)	10 (9.1)
Thrombocytopenia	11 (4.7)	10 (4.2)	11 (4.9)	6 (5.5)	4 (3.6)
Headache	8 (3.4)	11 (4.6)	8 (3.6)	4 (3.7)	7 (6.4)

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 26.0.

TEAEs by relatedness

For 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 group by PT, is summarised for the Safety set in **Table 52**.

The proportions of patients who experienced at least 1 TEAE considered by the investigator to be related to the study drug was similar between the CT-P47 and RoActemra groups (141 [60.3%] and 154 [65.0%] patients, respectively) and among the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups (136 [60.4%], 70 [64.2%], and 69 [62.7%] patients, respectively) (**Table 50**).

Table 52 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 (overall period): safety set.

	Initial Randomization		2nd Randomization		
	CT-P47 (N=234)	RoActemra (N=237)	CT-P47 Maintenance (N=225)	RoActemra Maintenance (N=109)	Switched to CT-P47 (N=110)
Preferred Term	**Number (%) of patients**				
Alanine aminotransferase increased	39 (16.7)	51 (21.5)	37 (16.4)	21 (19.3)	26 (23.6)
Neutropenia	25 (10.7)	34 (14.3)	23 (10.2)	13 (11.9)	19 (17.3)
Leukopenia	23 (9.8)	30 (12.7)	23 (10.2)	13 (11.9)	15 (13.6)
Upper respiratory tract infection	22 (9.4)	20 (8.4)	22 (9.8)	11 (10.1)	8 (7.3)
Aspartate aminotransferase increased	16 (6.8)	23 (9.7)	16 (7.1)	10 (9.2)	11 (10)
Hypercholesterolaemia	14 (6.0)	13 (5.5)	14 (6.2)	7 (6.4)	6 (5.5)
Transaminases increased	9 (3.8)	11 (4.6)	8 (3.6)	1 (0.9)	9 (8.2)
Lymphopenia	6 (2.6)	12 (5.1)	6 (2.7)	7 (6.4)	3 (2.7)
Thrombocytopenia	8 (3.4)	10 (4.2)	8 (3.6)	6 (5.5)	4 (3.6)

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 26.0.

TEAEs by intensity

During the Overall Period of the study, the majority of TEAEs were CTCAE grade 2 or 3 in intensity. A summary of Grade 3 or higher TEAEs in Study CT-P47 3.1 is displayed in **Table 53.**

There was one grade 5 TEAE of peritonitis in the CT-P47 maintenance group and none in the other groups. According to the CSR text, the reported grade 4 TEAEs were neutropenia (1 subject each in the CT-P47 and RoActemra groups), coronary artery stenosis (1 subject each in the RoActemra and the Switched to CT-P47 groups), myocardial ischaemia (1 subject in the RoActemra group and 1 subject in the Switched to CT-P47 group), and sepsis (1 subject in the RoActemra group and 1 subject in the RoActemra maintenance group), making in total eight (8) TEAEs of Grade 4.

Table 53 Summary of TEAEs by intensity of grade 3 or higher in study CT-P47 3.1 overall period. reported for >=1% of patients by PT in any treatment group by intensity of grade 3 or higher. (safety set and safety-treatment period II subset)

	Treatment Period I		Treatment Period II			Overall Period			
							RoActemra		
	CT-P47 (N=234)	RoActemra (N=237)	CT-P47 Maintenance (N=225)	RoActemra Maintenance (N=109)	Switched to CT-P47 (N=110)	CT-P47 (N=234)	Overall (N=237)	CT-P47 Maintenance (N=109)	RoActemra Maintenance (N=110)
Total Number of TEAEs of grade 3 or higher	31	41	26	17	13	57	71	32	28
Number of Patients with at Least 1 TEAE of grade 3 or higher	27 (11.5%)	32 (13.5%)	19 (8.4%)	12 (11.0%)	10 (9.1%)	43 (18.4%)	48 (20.3%)	19 (17.4%)	21 (19.1%)
Grade 3	26 (11.1%)	30 (12.7%)	18 (8%)	11 (10.1%)	10 (9.1%)	41 (17.5%)	45 (19.0%)	18 (16.5%)	20 (18.2%)
Grade 4	1 (0.4%)	2 (0.8%)	0	1 (0.9%)	0	1 (0.4%)	3 (1.3%)	1 (0.9%)	1 (0.9%)
Grade 5	0	0	1 (0.4%)	0	0	1 (0.4%)	0	0	0
Blood and lymphatic system disorders	7 (3.0%)	11 (4.6%)	4 (1.8%)	3 (2.8%)	3 (2.7%)	11 (4.7%)	15 (6.3%)	6 (5.5%)	8 (7.3%)
Neutropenia	7 (3.0%)	10 (4.2%)	3 (1.3%)	3 (2.8%)	3 (2.7%)	10 (4.3%)	14 (5.9%)	6 (5.5%)	7 (6.4%)
Investigations	5 (2.1%)	6 (2.5%)	3 (1.3%)	1 (0.9%)	1 (0.9%)	8 (3.4%)	7 (3.0%)	3 (2.8%)	2 (1.8%)
Alanine aminotransferase increased	2 (0.9%)	3 (1.3%)	1 (0.4%)	0	0	3 (1.3%)	3 (1.3%)	1 (0.9%)	0

Note: For SOC, the number and percentage of patients with at least 1 TEAE for each treatment period were summarised by SOC. For PT, only TEAEs reported for at least 2% of patients by PT in any treatment group were included. At each level of summarisation, patients were counted once if they reported one or more events. Only the most severe event was counted. The event was considered to be related if the relationship was defined as 'Possible', 'Probable', 'Definite'.
TEAEs in Treatment Period I and Overall Period were summarised for Safety Set and TEAEs in Treatment Period II was summarised for Safety-Treatment Period II subset.

Study CT-P47 3.2

In Study CT-P47 3.2, TEAEs were reported for 12 (36.4%) patients. The most frequently reported TEAEs by PT were leukopenia, neutropenia and injection site reaction (3 [9.1%] patients for each PT); all of these events were considered to be related to study drug. Grade 3 TEAEs were reported for 4 (12.1%) patients, with no events of Grade 4 or 5. The most frequently reported Grade 3 TEAE by PT was neutropenia for 2 (6.1%) patients.

Adverse events in healthy volunteer studies

In Study CT-P47 1.1 Part 1, TEAEs were reported for 5 (35.7%) and 7 (46.7%) subjects in the CT-P47 and EU-RoActemra groups, respectively. In Part 2, TEAEs were reported for 55 (38.2%) and 72 (51.4%) subjects in the CT-P47 and EU-RoActemra groups, respectively. In Study CT-P47 1.2, TEAEs were reported for 24 (53.3%), 24 (55.8%) and 24 (54.5%) subjects in the CT-P47, EU-RoActemra and US-Actemra groups, respectively. In Study CT-P47 1.3, TEAEs were reported for 82 (53.6%) and 77 (49.0%) subjects in the CT-P47 AI and CT-P47 PFS groups, respectively. An overview of TEAEs from the healthy volunteer studies is provided in **Table 54.**

Table 54 Overview of TEAEs in studies in healthy subjects (study CT-P47 1.1 part 1 and part 2 combined), study CT-P47 1.2 and study CT-P47 1.3 (safety set)

	Study CT-P47 1.1 (Healthy Subjects)		Study CT-P47 1.2 (Healthy Subjects)			Study CT-P47 1.3 (Healthy Subjects)	
	CT-P47 (N=158)	EU-RoActemra (N=155)	CT-P47 (N=45)	EU-RoActemra (N=43)	US-Actemra (N=44)	CT-P47 AI (N=153)	CT-P47 PFS (N=157)
Total number of TEAEs, n	109	145	32	44	37	158	164
Number (%) of subjects with ≥1 TEAE	60 (38.0)	79 (51.0)	24 (53.3)	24 (55.8)	24 (54.5)	82 (53.6)	77 (49.0)
Related	52 (32.9)	67 (43.2)	16 (35.6)	13 (30.2)	16 (36.4)	64 (41.8)	60 (38.2)
Unrelated	18 (11.4)	26 (16.8)	10 (22.2)	13 (30.2)	10 (22.7)	31 (20.3)	33 (21.0)
Number (%) of subjects with ≥1 TESAE	2 (1.3)	1 (0.6)	0	0	0	0	0
Related	0	1 (0.6)	0	0	0	0	0
Unrelated	2 (1.3)	0	0	0	0	0	0
Number (%) of subjects with ≥1 TEAE leading to study drug discontinuation	0	0	0	0	0	0	0
Number (%) of subjects with ≥1 TEAE leading to death	0	0	0	0	0	0	0
Number (%) of subjects with ≥1 TEAESI classified as infection	10 (6.3)	28 (18.1)	3 (6.7)	2 (4.7)	4 (9.1)	18 (11.8)	15 (9.6)
Related	5 (3.2)	19 (12.3)	0	0	1 (2.3)	13 (8.5)	13 (8.3)
Unrelated	5 (3.2)	9 (5.8)	3 (6.7)	2 (4.7)	3 (6.8)	5 (3.3)	2 (1.3)
Number (%) of subjects with ≥1 TEAESI classified as hypersensitivity reactions[1]	4 (2.5)	3 (1.9)	0	0	1 (2.3)	4 (2.6)	2 (1.3)
Related	4 (2.5)	3 (1.9)	0	0	1 (2.3)	4 (2.6)	2 (1.3)
Unrelated	0	0	0	0	0	0	0
Number (%) of subjects with ≥1 TEAESI classified as injection site reaction[2]	5 (3.2)	5 (3.2)	-	-	-	14 (9.2)	5 (3.2)
Related	5 (3.2)	5 (3.2)	-	-	-	14 (9.2)	5 (3.2)
Unrelated	0	0	-	-	-	0	0
Number (%) of subjects with ≥1 TEAESI classified as hepatic event	4 (2.5)	5 (3.2)	3 (6.7)	3 (7.0)	2 (4.5)	4 (2.6)	4 (2.5)
Related	2 (1.3)	2 (1.3)	1 (2.2)	1 (2.3)	2 (4.5)	2 (1.3)	0
Unrelated	2 (1.3)	4 (2.6)	2 (4.4)	2 (4.7)	0	2 (1.3)	4 (2.5)
Number (%) of subjects with ≥1 TEAESI classified as hemorrhage	2 (1.3)	0	0	1 (2.3)	0	2 (1.3)	3 (1.9)
Related	1 (0.6)	0	0	0	0	0	1 (0.6)
Unrelated	1 (0.6)	0	0	1 (2.3)	0	2 (1.3)	2 (1.3)
Number (%) of subjects with ≥1 TEAESI classified as gastrointestinal perforation, malignancy, or demyelinating disorder	0	0	0	0	0	0	0

Note: At each level of summarization of the number of subjects, a subject was counted once if one or more events were reported. The event was considered as related if the relationship was defined as 'possible', 'probable' or 'definite'.
[1] No subject experienced anaphylaxis based on Sampson's criteria during the study period
[2] In Study CT-P47 1.2, injection site reaction was not assessed since the study drug was administered via IV infusion

In Study CT-P47 1.1 Part 1, there were no individual PTs reported for more than one subject. In Part 2, the most frequently reported TEAE by PT, regardless of relationship to the study drug, was neutrophil count decreased (14 [9.7%] and 15 [10.7%] subjects in the CT-P47 and EU-RoActemra groups, respectively), followed by Coronavirus disease 2019 (COVID-19) (8 [5.6%] and 19 [13.6%] subjects, respectively). Other than COVID-19, there were no PTs with a greater than 3% difference between the treatment groups.

TEAEs considered to be related to study drug by the investigator were reported in 52 (32.9%) and 67 (43.2%) subjects in the CT-P47 and EU-RoActemra groups, respectively. The difference can partly be ascribed to a higher proportion of subjects with COVID-19 in the EU-RoActemra group (12 [8.6%] vs. 4 [2.8%] subjects in Part 2). In Part 2, the most frequently reported related TEAE by PT was neutrophil count decreased (14 [9.7%] and 15 [10.7%] subjects, respectively), followed by headache (7 [4.9%] and 10 [7.1%] subjects, respectively).

In Study CT-P47 1.1 Part 1, all TEAEs were Grade 1 in intensity except for 3 cases: Grade 3 TEAE of blood creatine phosphokinase (CPK) increased was reported for 1 (7.1%) subject in the CT-P47 group

and Grade 4 TEAEs of neutropenia and hypertriglyceridaemia were reported in 1 (6.7%) subject each in the EU-RoActemra group. In Part 2, Grade 3 TEAEs were reported for 4 (2.8%) and 8 (5.7%) subjects, and Grade 4 TEAEs for 3 (2.1%) and 4 (2.9%) subjects, in the CT-P47 and EU-RoActemra groups, respectively. The most frequently reported Grade 3 or higher TEAE by PT was neutrophil count decreased (4 [2.8%] and 7 [5.0%] subjects for CT-P47 and EU-RoActemra groups, respectively; all events considered related to study drug). Grade 4 blood CPK increased was reported for 2 (1.4%) subjects in both groups, with all other Grade 3-4 events being single occurrences at the PT level. Grade 3-4 events were not reported in the SOC 'Infections and infestations'.

A summary of TEAEs by SOC and PT reported for 2% or more subjects in Part 2 of Study CT-P47 1.1 is displayed in **Table 55**.

Table 55 Summary of TEAEs by SOC and PT in study CT-P47 1.1 – part 2 (safety set). Note that at PT level, only those reported for ≥2% of subjects in any treatment group are shown in the table.

SOC PT	CT-P47 (N=144)	EU-RoActemra (N=140)
Total Number of TEAEs	**103**	**134**
Number (%) of subjects with at least 1 TEAE	**55 (38.2)**	**72 (51.4)**
Related	47 (32.6)	61 (43.6)
Unrelated	18 (12.5)	25 (17.9)
Gastrointestinal disorders	**5 (3.5)**	**14 (10.0)**
Diarrhoea	1 (0.7)	3 (2.1)
Nausea	3 (2.1)	2 (1.4)
General disorders and administration site conditions	**16 (11.1)**	**10 (7.1)**
Injection site reaction	4 (2.8)	5 (3.6)
Immune system disorders	**4 (2.8)**	**2 (1.4)**
Hypersensitivity	4 (2.8)	2 (1.4)
Infections and infestations	**10 (6.9)**	**25 (17.9)**
COVID-19	8 (5.6)	19 (13.6)
Injury, poisoning and procedural complications	**4 (2.8)**	**6 (4.3)**
Ligament sprain	1 (0.7)	4 (2.9)
Investigations	**17 (11.8)**	**23 (16.4)**
Alanine aminotransferase increased	2 (1.4)	3 (2.1)
Aspartate aminotransferase increased	2 (1.4)	3 (2.1)
Neutrophil count decreased	14 (9.7)	15 (10.7)
White blood cell count decreased	8 (5.6)	6 (4.3)
Musculoskeletal and connective tissue disorders	**3 (2.1)**	**10 (7.1)**
Arthralgia	0	3 (2.1)
Nervous system disorders	**9 (6.3)**	**13 (9.3)**
Headache	7 (4.9)	11 (7.9)
Respiratory, thoracic and mediastinal disorders	**7 (4.9)**	**4 (2.9)**
Cough	4 (2.8)	1 (0.7)
Oropharyngeal pain	4 (2.8)	1 (0.7)

Note: Only TEAEs reported for at least 2% of patients by PT in any treatment group were included. The total number of TEAEs count includes all subject events. At each level of summarization of the number of subjects, a subject was counted once if one or more events were reported. The event was considered as related if the relationship was defined as 'possible', 'probable' or 'definite'.

In Study CT-P47 1.2, the most frequently reported TEAE by PT, regardless of relationship to the study drug, was neutrophil count decreased (15 [33.3%], 13 [30.2%] and 12 [27.3%] subjects in the CT-P47, EU-RoActemra and US-Actemra groups, respectively), followed by white blood cell count decreased (3 [6.7%], 4 [9.3%] and 3 [6.8%] subjects, respectively).

TEAEs considered to be related to study drug by the investigator were reported in 16 (35.6%), 13 (30.2%) and 16 (36.4%) subjects in the CT-P47, EU-RoActemra and US-Actemra groups, respectively. The most frequently reported related TEAE by PT was neutrophil count decreased (15 [33.3%], 13 [30.2%] and 12 [27.3%] subjects, respectively), followed by white blood cell count decreased (3 [6.7%], 4 [9.3%] and 3 [6.8%] subjects, respectively).

Grade 3 TEAEs were reported for 15 (33.3%), 11 (25.6%) and 11 (25.0%) subjects, and Grade 4 TEAEs for 1 (2.2%), 4 (9.3%) and 4 (9.1%) subjects in the CT-P47, EU-RoActemra and US-Actemra groups, respectively. The Grade 4 TEAEs comprised PTs of neutrophil count decreased (1, 4 and 3 subjects on CT-P47, EU-RoActemra and US-Actemra, respectively) and blood CPK decreased (1 subject on US-Actemra). The most frequently reported Grade 3 or higher TEAE by PT was neutrophil count decreased (15 [33.3%], 13 [30.2%] and 12 [27.3%] subjects, respectively). Grade 3-4 events were not reported in the SOC 'Infections and infestations'.

A summary of TEAEs by SOC and PT reported for 2% or more subjects in Study CT-P47 1.2 is displayed in **Table 56**.

Table 56 Summary of TEAEs by SOC and PT in study CT-P47 1.2 (safety set). Note that at PT level, only those reported for ≥2% of subjects in any treatment group are shown in the table.

SOC PT	CT-P47 (N=45)	EU-RoActemra (N=43)	US-Actemra (N=44)
Total Number of TEAEs	**32**	**44**	**37**
Number (%) of subjects with at least 1 TEAE	**24 (53.3)**	**24 (55.8)**	**24 (54.5)**
Related	16 (35.6)	13 (30.2)	16 (36.4)
Unrelated	10 (22.2)	13 (30.2)	10 (22.7)
Gastrointestinal disorders	**1 (2.2)**	**4 (9.3)**	**0**
Abdominal discomfort	0	1 (2.3)	0
Enterocolitis	0	1 (2.3)	0
Glossodynia	1 (2.2)	0	0
Stomatitis	0	1 (2.3)	0
Toothache	0	1 (2.3)	0
General disorders and administration site conditions	**0**	**2 (4.7)**	**1 (2.3)**
Malaise	0	0	1 (2.3)
Pyrexia	0	2 (4.7)	0
Hepatobiliary disorders	**1 (2.2)**	**0**	**1 (2.3)**
Hepatic function abnormal	1 (2.2)	0	1 (2.3)
Immune system disorders	**3 (6.7)**	**2 (4.7)**	**2 (4.5)**
Hypersensitivity	0	0	1 (2.3)
Seasonal allergy	3 (6.7)	2 (4.7)	1 (2.3)
Infections and infestations	**3 (6.7)**	**2 (4.7)**	**4 (9.1)**
Gastroenteritis	0	1 (2.3)	1 (2.3)
Nasopharyngitis	1 (2.2)	1 (2.3)	1 (2.3)
Pharyngitis	0	0	1 (2.3)
Upper respiratory tract infection	2 (4.4)	0	1 (2.3)
Injury, poisoning and procedural complications	**0**	**2 (4.7)**	**0**
Contusion	0	1 (2.3)	0
Post-traumatic pain	0	1 (2.3)	0
Investigations	**17 (37.8)**	**20 (46.5)**	**16 (36.4)**
Alanine aminotransferase increased	2 (4.4)	1 (2.3)	1 (2.3)
Aspartate aminotransferase increased	0	1 (2.3)	1 (2.3)
Blood bilirubin increased	0	2 (4.7)	1 (2.3)
Blood cholesterol increased	0	0	1 (2.3)
Blood creatine phosphokinase increased	2 (4.4)	2 (4.7)	2 (4.5)
Blood triglycerides increased	0	1 (2.3)	0
C-reactive protein increased	0	2 (4.7)	1 (2.3)
Low density lipoprotein increased	0	0	1 (2.3)
Neutrophil count decreased	15 (33.3)	13 (30.2)	12 (27.3)
White blood cell count decreased	3 (6.7)	4 (9.3)	3 (6.8)
White blood cell count increased	0	1 (2.3)	0
Metabolism and nutrition disorders	**0**	**0**	**1 (2.3)**
Hypertriglyceridaemia	0	0	1 (2.3)

Table 55 continued Summary of TEAEs by SOC and PT in study CT-P47 1.2 (safety set). Note that at PT level, only those reported for ≥2% of subjects in any treatment group are shown in the table.

SOC PT	CT-P47 (N=45)	EU-RoActemra (N=43)	US-Actemra (N=44)
Nervous system disorders	**0**	**2 (4.7)**	**1 (2.3)**
Headache	0	1 (2.3)	1 (2.3)
Presyncope	0	1 (2.3)	0
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**1 (2.3)**
Oropharyngeal discomfort	0	0	1 (2.3)
Rhinorrhoea	0	0	1 (2.3)
Skin and subcutaneous tissue disorders	**1 (2.2)**	**0**	**2 (4.5)**
Acne	1 (2.2)	0	0
Eczema	0	0	1 (2.3)
Rash	0	0	1 (2.3)

Note: Only TEAEs reported for at least 2% of patients by PT in any treatment group were included. The total number of TEAEs count includes all subject events. At each level of summarization of the number of subjects, a subject was counted once if one or more events were reported. The event was considered as related if the relationship was defined as 'possible', 'probable' or 'definite'.

In Study CT-P47 1.3, the most frequently reported TEAE by PT, regardless of relationship to the study drug, was neutrophil count decreased (23 [15.0%] and 14 [8.9%] subjects in the CT-P47 AI and CT P47 PFS groups, respectively); decreased white cell count was also more frequent in the AI group (10 [6.5%] vs. 4 [2.5%] subjects in the AI and PFS groups, respectively). Injection site reactions were reported for 14 (9.2%) and 5 (3.2%) subjects in the AI and PFS groups, respectively. According to the applicant, the higher proportion of injection site reactions in the CT-P47 AI group could be explained by a relatively higher pressure applied with the AI against the skin.

TEAEs considered to be related to study drug by the investigator were reported in 64 (41.8%) and 60 (38.2%) subjects in the CT-P47 AI and CT P47 PFS groups, respectively. The most frequently reported related TEAE by PT was neutrophil count decreased (23 [15.0%] and 14 [8.9%] subjects, respectively), followed by injection site reaction (14 [9.2%] and 5 [3.2%] subjects, respectively). All injection site reactions were grade 1 or 2 in intensity and resolved without treatment within the day except for 1 subject each in both treatment groups.

Grade 3 or higher TEAEs were reported for 12 (7.8%) and 14 (8.9%) subjects in the CT-P47 AI and CT-P47 PFS groups, respectively. The most frequently reported Grade 3 or higher TEAE by PT was neutrophil count decreased (7 [4.6%] and 6 [3.8%] subjects, respectively). Grade 3-4 events were not reported in the SOC 'Infections and infestations'.

A summary of TEAEs by SOC and PT reported for 2% or more subjects in Study CT-P47 1.3 is displayed in **Table 57**, and Grade 3 or higher TEAEs are summarised in **Table 58**.

Table 57 Summary of TEAEs by SOC and PT in study CT-P47 1.3 (safety set). Note that at PT level, only those reported for ≥2% of subjects in any treatment group are shown in the table.

SOC PT	CT-P47 AI (N=153)	CT-P47 PFS (N=157)
Total Number of TEAEs	**158**	**164**
Number (%) of subjects with at least 1 TEAE	**82 (53.6)**	**77 (49.0)**
Related	64 (41.8)	60 (38.2)
Unrelated	31 (20.3)	33 (21.0)
Gastrointestinal disorders	**8 (5.2)**	**7 (4.5)**
Diarrhoea	4 (2.6)	3 (1.9)
General disorders and administration site conditions	**20 (13.1)**	**13 (8.3)**
Injection site reaction	14 (9.2)	5 (3.2)
Immune system disorders	**4 (2.6)**	**3 (1.9)**
Hypersensitivity	4 (2.6)	3 (1.9)
Infections and infestations	**18 (11.8)**	**15 (9.6)**
COVID-19	5 (3.3)	3 (1.9)
Upper respiratory tract infection	7 (4.6)	4 (2.5)
Investigations	**40 (26.1)**	**32 (20.4)**
Alanine aminotransferase increased	4 (2.6)	2 (1.3)
Blood creatine phosphokinase increased	0	4 (2.5)
Blood phosphorus increased	6 (3.9)	2 (1.3)
Blood pressure diastolic increased	2 (1.3)	6 (3.8)
Blood triglycerides increased	2 (1.3)	4 (2.5)
Neutrophil count decreased	23 (15.0)	14 (8.9)
White blood cell count decreased	10 (6.5)	4 (2.5)
Nervous system disorders	**7 (4.6)**	**15 (9.6)**
Dizziness	2 (1.3)	4 (2.5)
Headache	5 (3.3)	8 (5.1)
Respiratory, thoracic and mediastinal disorders	**12 (7.8)**	**18 (11.5)**
Cough	5 (3.3)	6 (3.8)
Oropharyngeal pain	4 (2.6)	6 (3.8)
Rhinorrhoea	3 (2.0)	6 (3.8)

Note: Only TEAEs reported for at least 2% of patients by PT in any treatment group were included. The total number of TEAEs count includes all subject events. At each level of summarization of the number of subjects, a subject was counted once if one or more events were reported. The event was considered as related if the relationship was defined as 'possible', 'probable' or 'definite'.

Table 58 Summary of TEAEs by intensity of grade 3 or higher in study CT-P47 1.3 (safety set)

SOC PT	CT-P47 AI (N=153)	CT-P47 PFS (N=157)
Number (%) of subjects with at least 1 TEAE of grade 3 or higher	**12 (7.8)**	**14 (8.9)**
Grade 3	10 (6.5)	6 (3.8)
Grade 4	2 (1.3)	8 (5.1)
Grade 3 or higher TEAEs by SOC/PT		
Infections and infestations	**18 (11.8)**	**15 (9.6)**
COVID-19 – grade 3, Unrelated	2 (1.3)	0
Investigations	**40 (26.1)**	**32 (20.4)**
Blood creatine phosphokinase increased – grade 3, Unrelated	0	1 (0.6)
Blood creatine phosphokinase increased – grade 4, Unrelated	0	3 (1.9)
Blood potassium increased – grade 3, Unrelated	1 (0.7)	0
Blood triglycerides increased – grade 3, Unrelated	0	3 (1.9)
Blood triglycerides increased – grade 4, Unrelated	1 (0.7)	1 (0.6)
Neutrophil count decreased – grade 3, Related	6 (3.9)	2 (1.3)
Neutrophil count decreased – grade 4, Related	1 (0.7)	4 (2.5)
White blood cell count decreased – grade 3, Related	1 (0.7)	2 (1.3)
Musculoskeletal and connective tissue disorders	**3 (2.0)**	**3 (1.9)**
Rhabdomyolysis – grade 3, Related	0	1 (0.6)
Nervous system disorders	**7 (4.6)**	**15 (9.6)**
Headache – grade 3, Related	1 (0.7)	0

Note: For SOC, the number and percentage of patients with at least 1 TEAE of grade 3 or higher for each treatment group were summarized by SOC. For PT, only grade 3 of higher TEAEs by PT in any treatment group were included. At each level of summarization of the number of subjects, a subject was counted once if one or more events were reported. Only the most severe event was counted.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

In Study CT-P47 3.1, 1 (0.4%) patient died due to a TEAE of grade 5 peritonitis in the CT-P47 maintenance group during Treatment Period II. Peritonitis occurred after gastroscopy for medical work-up. The death was also included in the categories of TEAEs classified as infection and gastrointestinal perforation (grade 5 peritonitis, unrelated). The event of peritonitis was considered to be unrelated to the study drug by the investigator.

No deaths were reported in any of the other studies.

Other SAEs in studies in RA patients

All TESAEs in Treatment Period I, Treatment Period II and Overall Period in Study CT-P47 3.1 are summarised by SOC and PT in **Table 59**. There were no notable differences in TESAEs among the treatment groups throughout the study periods. Based on PT, most TESAEs were reported for no more than 1 patient in any of the group and the majority of TESAEs were grade 2 or 3 in intensity. All TESAEs were considered to be unrelated to the study drug by the investigator except for the events of erysipelas (1 patient in the EU-RoActemra group) and pneumonia/respiratory failure, interferon gamma release assay positive, syncope and venous thrombosis limb (1 patient each in the CT-P47 and CT-P47 maintenance groups).

Table 59 Summary of TESAEs by SOC and PT in study CT-P47 3.1, overall period (safety set and safety-treatment period II subset).

	Treatment Period I		Treatment Period II			Overall Period			
							RoActemra		
	CT-P47 (N=234)	RoActemra (N=237)	CT-P47 Maintenance (N=225)	RoActemra Maintenance (N=109)	Switched to CT-P47 (N=110)	CT-P47 (N=234)	Overall (N=237)	CT-P47 Maintenance (N=109)	RoActemra Maintenance (N=110)
General disorders and administration site conditions	1 (0.4%)	0	0	1 (0.9%)	0	1 (0.4%)	1 (0.4%)	1 (0.9%)	0
Chest pain	0	0	0	1 (0.9%)	0	0	1 (0.4%)	1 (0.9%)	0
Peripheral swelling	1 (0.4%)	0	0	0	0	1 (0.4%)	0	0	0
Hepatobiliary disorders	0	0	1 (0.4%)	0	0	1 (0.4%)	0	0	0
Cholelithiasis	0	0	1 (0.4%)	0	0	1 (0.4%)	0	0	0
Infections and infestations	3 (1.3%)	2 (0.8%)	2 (0.9%)	2 (1.8%)	0	5 (2.1%)	4 (1.7%)	2 (1.8%)	1 (0.9%)
Arthritis bacterial	0	0	0	1 (0.9%)	0	0	1 (0.4%)	1 (0.9%)	0
COVID-19 pneumonia	1 (0.4%)	0	0	0	0	1 (0.4%)	0	0	0
Erysipelas	0	1 (0.4%)	0	0	0	0	1 (0.4%)	0	1 (0.9%)
Lyme disease	1 (0.4%)	0	0	0	0	1 (0.4%)	0	0	0
Peritonitis	0	0	1 (0.4%)	0	0	1 (0.4%)	0	0	0
Pneumonia	0	0	1 (0.4%)	0	0	1 (0.4%)	0	0	0
Pyelonephritis	1 (0.4%)	0	0	0	0	1 (0.4%)	0	0	0
Sepsis	0	0	0	1 (0.9%)	0	0	1 (0.4%)	1 (0.9%)	0
Urosepsis	0	1 (0.4%)	0	0	0	0	1 (0.4%)	0	0
Injury, poisoning and procedural complications	0	1 (0.4%)	3 (1.3%)	3 (2.8%)	1 (0.9%)	3 (1.3%)	5 (2.1%)	3 (2.8%)	2 (1.8%)
Ankle fracture	0	0	1 (0.4%)	0	1 (0.9%)	1 (0.4%)	1 (0.4%)	0	1 (0.9%)
Femoral neck fracture	0	0	0	1 (0.9%)	0	0	1 (0.4%)	1 (0.9%)	0
Femur fracture	0	1 (0.4%)	1 (0.4%)	0	0	1 (0.4%)	1 (0.4%)	0	1 (0.9%)
Humerus fracture	0	0	0	1 (0.9%)	0	0	1 (0.4%)	1 (0.9%)	0
Radius fracture	0	0	0	1 (0.9%)	0	0	1 (0.4%)	1 (0.9%)	0
Tendon rupture	0	0	0	1 (0.9%)	0	0	1 (0.4%)	1 (0.9%)	0
Upper limb fracture	0	0	1 (0.4%)	0	0	1 (0.4%)	0	0	0
Investigations	0	0	1 (0.4%)	0	0	1 (0.4%)	0	0	0
Interferon gamma release assay positive	0	0	1 (0.4%)	0	0	1 (0.4%)	0	0	0
Musculoskeletal and connective tissue disorders	1 (0.4%)	0	0	1 (0.9%)	2 (1.8%)	1 (0.4%)	3 (1.3%)	1 (0.9%)	2 (1.8%)
Bone loss	1 (0.4%)	0	0	0	0	1 (0.4%)	0	0	0
Fracture nonunion	0	0	0	0	1 (0.9%)	0	1 (0.4%)	0	1 (0.9%)
Osteoarthritis	0	0	0	1 (0.9%)	0	0	1 (0.4%)	1 (0.9%)	0
Rheumatoid arthritis	0	0	0	0	1 (0.9%)	0	1 (0.4%)	0	1 (0.9%)

Table 58 continued Summary of TESAEs by SOC and PT in study CT-P47 3.1, overall period (safety set and safety-TP II subset)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.4%)	0	1 (0.9%)	0	0	2 (0.8%)	1 (0.9%)	0
Meningioma benign	0	0	0	1 (0.9%)	0	0	1 (0.4%)	1 (0.9%)	0
Pancreatic neoplasm	0	1 (0.4%)	0	0	0	0	1 (0.4%)	0	0
Nervous system disorders	0	1 (0.4%)	1 (0.4%)	0	2 (1.8%)	1 (0.4%)	3 (1.3%)	0	2 (1.8%)
Cerebrovascular disorder	0	0	0	0	1 (0.9%)	0	1 (0.4%)	0	1 (0.9%)
Headache	0	0	0	0	1 (0.9%)	0	1 (0.4%)	0	1 (0.9%)
Monoparesis	0	1 (0.4%)	0	0	0	0	1 (0.4%)	0	0
Syncope	0	0	1 (0.4%)	0	0	1 (0.4%)	0	0	0
Psychiatric disorders	1 (0.4%)	0	0	0	0	1 (0.4%)	0	0	0
Schizophrenia	1 (0.4%)	0	0	0	0	1 (0.4%)	0	0	0
Reproductive system and breast disorders	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	1 (0.9%)	2 (0.9%)	2 (0.8%)	0	2 (1.8%)
Cervical cyst	1 (0.4%)	0	0	0	0	1 (0.4%)	0	0	0
Endometrial hyperplasia	0	1 (0.4%)	0	0	0	0	1 (0.4%)	0	1 (0.9%)
Rectocele	0	0	1 (0.4%)	0	0	1 (0.4%)	0	0	0
Uterine haemorrhage	0	0	0	0	1 (0.9%)	0	1 (0.4%)	0	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	1 (0.4%)	0	2 (0.9%)	0	1 (0.9%)	3 (1.3%)	1 (0.4%)	0	1 (0.9%)
Interstitial lung disease	0	0	0	0	1 (0.9%)	0	1 (0.4%)	0	1 (0.9%)
Pleural effusion	1 (0.4%)	0	0	0	0	1 (0.4%)	0	0	0
Pulmonary embolism	0	0	1 (0.4%)	0	0	1 (0.4%)	0	0	0
Respiratory failure	0	0	1 (0.4%)	0	0	1 (0.4%)	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	0	1 (0.9%)	0	1 (0.4%)	0	1 (0.9%)
Dermatitis	0	0	0	0	1 (0.9%)	0	1 (0.4%)	0	1 (0.9%)
Vascular disorders	1 (0.4%)	1 (0.4%)	0	0	0	1 (0.4%)	1 (0.4%)	0	0
Extremity necrosis	0	1 (0.4%)	0	0	0	0	1 (0.4%)	0	0
Venous thrombosis limb	1 (0.4%)	0	0	0	0	1 (0.4%)	0	0	0

Note: At each level of summarisation, patients were counted once if they reported one or more events. Only the most severe event was counted. The event was considered to be related if the relationship was defined as 'Possible', 'Probable', 'Definite'.
TEAEs in Treatment Period I and Overall Period were summarised for Safety Set and TEAEs in Treatment Period II was summarised for Safety-Treatment Period II subset.

In Study CT-P47 3.2, a case of cerebrovascular disorder which was considered by the investigator to be possibly related to the study drug was reported for 1 (3.0%) patient, a 61-year-old female who was given the first dose of study drug on April 2023. Final diagnosis was reported as abnormalities of cerebral circulation with a history of seizure episode. The event of cerebrovascular disorder was considered to be resolved on May 2023. The patient discontinued the study drug and ended study participation on Apr 2023 due to the patient's withdrawal from the study. At the time of last report, the investigator confirmed that only the discharge chart could be provided and no more data was available due to the patient's withdrawal of consent.

Other SAEs in healthy volunteer studies

In Study CT-P47 1.1, there were no TESAEs in Part 1. In Part 2, TESAEs were reported for 2 (1.4%) subjects in the CT-P47 group and 1 (0.7%) subject in the EU-RoActemra group. Among the 3 subjects, two grade 2 TESAEs (COVID-19 and Pain in extremity), considered unrelated to study drug, were reported in the CT-P47 group, and a grade 3 TESAE of headache, which was considered possibly related to the study drug, was reported in the EU-RoActemra group. All TESAEs recovered with medication and/or non-medication treatment.

There were no TESAEs in Study CT-P47 1.2 or Study CT-P47 1.3.

Adverse events of special interest

For the safety analyses, the following AESIs were defined: an event of infection, hypersensitivity reactions including anaphylaxis, hepatic event, haemorrhage (medically significant bleeding events), gastrointestinal perforation, malignancy and demyelinating disorder for all studies. Injection site reactions were considered an AESI only for SC Studies CT-P47 3.2, CT-P47 1.1 and CT-P47 1.3. According to the applicant, the selection was based on the known safety profile of tocilizumab, considering the adverse reactions presented in the SmPC of the reference product and other available clinical information.

Infections

Studies in RA patients

Study CT-P47 3.1

In TP I, there was a higher total number of TEAEs classified as infection in the CT-P47 group vs. the RoActemra group: 156 events/234 subjects vs. 124 events/237 subjects, respectively. Additionally, a higher proportion of subjects were reported to have an infection compared to the RoActemra group (110/234 [47.0%] for CT-P47 and 86/237 [36.3%] for RoActemra) with most of the difference coming from the imbalance in upper respiratory tract infections (URTI), which is a very commonly (≥1/10) reported adverse drug event according to the RoActemra SmPC. All events of URTI were reported as non-serious and non-severe except for 1 grade 3 non-serious event, and all these events were resolved without sequelae. Grade 3 related infections were reported in a small and same number of patients between the treatment groups (2 [0.9%] and 2 [0.8%] patients, in the CT-P47 and RoActemra groups, respectively). There were no opportunistic infections and active TB cases reported. During TP II, the number (%) of patients with reported infection was 64/87 (28.4%), 32/109 (29.4%) and 31/110 (28.2%) in the CT-P47 maintenance, RoActemra maintenance, and Switched to CT-P47 groups, respectively. There were no new infections when compared to the known safety profile of tocilizumab. Since the proportion of subjects with infections was balanced during TP II, the slight imbalance in the incidence of infections during TP I is considered to be likely due to chance (**Table *60***).

Table 60 Treatment-emergent adverse events (TEAEs) classified as infection reported for ≥2% of patients in either group using preferred term in treatment periods I and II (safety set and safety-treatment period II subset).

	Treatment Period I		Treatment Period II		
System Organ Class	**CT-P47 (N=234)**	**RoActemra (N=237)**	**CT-P47 maintenance (N=225)**	**RoActemra maintenance (N=109)**	**Switched to CT-P47 (N=110)**
Preferred term	**Number (%) of Patients**				
Total Number of TEAEs classified as Infection	**156**	**123**	**87**	**42**	**38**
Infections and Infestations	**110 (47.0)**	**86 (36.3)**	**64 (28.4)**	**32 (29.4)**	**31 (28.2)**
Upper respiratory tract infection	50 (21.4)	40 (16.9)	16 (7.1)	10 (9.2)	8 (7.3)
Nasopharyngitis	18 (7.7)	20 (8.4)	8 (3.6)	2 (1.8)	4 (3.6)
Pharyngitis	9 (3.8)	4 (1.7)	5 (2.2)	4 (3.7)	4 (3.6)
Tonsillitis	7 (3.0)	0	4 (1.8)	1 (0.9)	1 (0.9)
Sinusitis	6 (2.6)	6 (2.5)	5 (2.2)	0	1 (0.9)
Bronchitis	5 (2.1)	5 (2.1)	2 (0.9)	4 (3.7)	3 (2.7)
Urinary tract infection	4 (1.7)	5 (2.1)	3 (1.3)	3 (2.8)	1 (0.9)
Oral herpes	3 (1.3)	3 (1.3)	4 (1.8)	4 (3.7)	2 (1.8)
Latent tuberculosis	0	0	16 (7.1)	3 (2.8)	5 (4.5)

The first IGRA test after start of study drug was at Week 24. Latent TB was defined as a positive result of IGRA (in a subject with negative IGRA at baseline) with negative examination of chest X-ray. An imbalance was noted in incidence of latent TB during TP II and on the other hand no latent TB cases were reported for TP I. The applicant explained that no latent tuberculosis cases were reported during TP I, since according to the protocol, the IGRA test was performed at Week 24 pre-dose (included in Treatment Period I), but even when the result was positive, all TEAEs of latent TB were included in Treatment Period II summary (on or after the date of first study drug administration in Treatment Period II) because the start time of latent TB was not collected and TEAEs for Treatment Period II were classified based on the start date.

In final data up to Week 52, there was a numerical imbalance in cases with latent tuberculosis during TP II. A total of 24 (5.4%) patients (16 [7.1%], 3 [2.8%], and 5 [4.5%] patients in the CT-P47 maintenance group, the RoActemra maintenance group, and the switched to CT-P47 group, respectively) reported TEAE of latent TB. All latent TB cases were of Grade 1 or 2.

Study CT-P47 3.2

A TEAE classified as infection was reported for 4 (12.1%) patients. All TEAEs classified as infections were grade 1 or 2 in intensity. The most frequently reported TEAE classified as infection was upper respiratory tract infection (2 [6.1%] patients).

Healthy volunteer studies

Study CT-P47 1.1

In Study CT-P47 1.1 Part 1, TEAEs classified as infection were reported for 3 (20.0%) subjects in the EU-RoActemra group only. No serious infections were reported, and all of the subjects recovered from the event.

In Study CT-P47 1.1 Part 2, TEAEs classified as infection were reported for 10 (6.9%) and 25 (17.9%) subjects in the CT-P47 and EU-RoActemra groups, respectively. The difference between the two treatment groups is mainly from higher number of COVID-19 infection in the EU-RoActemra groups (8 [5.6%] and 19 [13.6%] subjects, respectively); COVID-19 is also the most frequently reported TEAE classified as infection. According to the applicant, COVID 19 infection cases should be interpreted in the context that the study period was at the peak of the COVID-19 incidence in South Korea where the study was conducted. All TEAEs classified as infections were grade 1 or 2 in intensity. All other TEAEs classified as infection were reported by no more than 1% of subjects in total. No serious infections were reported except for 1 (0.7%) subject with COVID-19 in the CT-P47 group. All of the subjects recovered from the event except 1 event of COVID-19 in the CT-P47 group for which the outcome was reported as unknown; the event was ongoing at the last visit on Day 43.

Study CT-P47 1.2

In Study CT-P47 1.2, TEAEs classified as infection were reported for 3 (6.7%), 2 (4.7%) and 4 (9.1%) subjects in the CT-P47, EU-RoActemra and US-Actemra groups, respectively. All TEAEs classified as infections were grade 1 or 2 in intensity. The most frequently reported TEAEs classified as infection included nasopharyngitis (1 [2.2%], 1 [2.3%] and 1 [2.3%] subjects, respectively) and upper respiratory tract infection (2 [4.4%] and 1 [2.3%] subjects in the CT-P47 and US-Actemra groups, respectively). No serious infections were reported and all of the subjects recovered from the event.

Study CT-P47 1.3

In Study CT-P47 1.3, TEAEs classified as infection were reported for 18 (11.8%) and 15 (9.6%) subjects in the CT-P47 AI and CT P47 PFS groups, respectively. All TEAEs classified as infections were grade 1 or 2 in intensity except for 2 grade 3 TEAEs of COVID-19 in the CT-P47 AI group. The most frequently reported TEAE classified as infection was upper respiratory tract infection (7 [4.6%] and 4 [2.5%] subjects, respectively), followed by COVID-19 (5 [3.3%] and 3 [1.9%] subjects, respectively). No serious infections were reported. All of the subjects recovered from the event and 1 (0.6%) subject in the CT-P47 PFS group was recovering at the time of database lock.

Hypersensitivity reactions

Studies in RA patients

Study CT-P47 3.1

All TEAEs classified as hypersensitivity reactions in Treatment Period I, Treatment Period II and Overall Period are summarised by relationship and intensity for the Safety Set in **Table 61**.

Overall, 11 (2.3%) patients experienced at least 1 TEAE classified as hypersensitivity reactions. The proportion of patients who experienced at least 1 TEAE classified as hypersensitivity reactions was

similar between CT-P47 and RoActemra groups (4 [1.7%] and 7 [3.0%] patients in the CT-P47 and RoActemra groups, respectively, and 4 [1.8%], 1 [0.9%], and 1 [0.9%] patients in the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups, respectively).

Most TEAEs were grade 1 or 2 in intensity except for 2 cases. During TP I, 1 patient in the EU-RoActemra group experienced a grade 3 hypersensitivity reaction during Treatment Period I which was classified as anaphylaxis. This patient experienced rash, hypotension, and electrocardiogram QT prolonged after Week 8 study drug administration and discontinued the study drug due to this event. During TP II, there was one TEAE classified as hypersensitivity reaction in the CT-P47 maintenance group. The patient experienced grade 3 hypersensitivity reaction with the signs and symptoms of hypertension (grade 1) and urticaria (grade 3) after Week 40 study drug administration. The patient recovered with medication treatment on the date of event but discontinued the study drug due to this event.

The most frequently reported sign and symptom was rash, reported in 2 (0.9%) and 5 (2.1%) patients in the CT-P47 and EU-RoActemra groups, respectively, both during TP I. All patients with hypersensitivity reactions recovered from the event with or without treatment except for 1 patient in the EU-RoActemra group with an unknown outcome.

Table 61 Treatment-emergent adverse events classified as hypersensitivity reactions by relationship and intensity in study CT-P47 3.1 (safety set/safety-treatment period II subset)

	Treatment Period I		Treatment Period II			Overall Period			
							RoActemra		
	CT-P47 (N=234)	RoActemra (N=237)	CT-P47 Maintenance (N=225)	RoActemra Maintenance (N=109)	Switched to CT-P47 (N=110)	CT-P47 (N=234)	Overall (N=237)	CT-P47 Maintenance (N=109)	RoActemra Maintenance (N=110)
Total Number of TEAEs classified as hypersensitivity reactions	5	8	1	0	0	6	8	1	1
Number of Patients with at Least 1 TEAE classified as hypersensitivity reactions	3 (1.3%)	7 (3.0%)	1 (0.4%)	0	0	4 (1.7%)	7 (3.0%)	1 (0.9%)	1 (0.9%)
Related	3 (1.3%)	7 (3.0%)	1 (0.4%)	0	0	4 (1.7%)	7 (3.0%)	1 (0.9%)	1 (0.9%)
Immune system disorders	3 (1.3%)	7 (3.0%)	1 (0.4%)	0	0	4 (1.7%)	7 (3.0%)	1 (0.9%)	1 (0.9%)
Hypersensitivity	3 (1.3%)	7 (3.0%)	1 (0.4%)	0	0	4 (1.7%)	7 (3.0%)	1 (0.9%)	1 (0.9%)
Related	3 (1.3%)	7 (3.0%)	1 (0.4%)	0	0	4 (1.7%)	7 (3.0%)	1 (0.9%)	1 (0.9%)
Grade 1	2 (0.9%)	0	0	0	0	2 (0.9%)	0	0	0
Grade 2	1 (0.4%)	6 (2.5%)	0	0	0	1 (0.4%)	6 (2.5%)	1 (0.9%)	1 (0.9%)
Grade 3	0	1 (0.4%)	1 (0.4%)	0	0	1 (0.4%)	1 (0.4%)	0	0

Note: At each level of summarisation, patients were counted once if they reported one or more events. Only the most severe event was counted. The event was considered to be related if the relationship was defined as 'Possible', 'Probable', 'Definite'.
TEAEs in Treatment Period I and Overall Period were summarised for Safety Set and TEAEs in Treatment Period II was summarised for Safety-Treatment Period II subset.

Study CT-P47 3.2

In Study CT-P47 3.2, there were no TEAEs classified as hypersensitivity including anaphylaxis.

Healthy volunteer studies

Study CT-P47 1.1

In Study CT-P47 1.1 Part 1, a TEAE classified as a hypersensitivity reaction was reported for 1 (6.7%) subject in the EU-RoActemra group with signs and symptoms of rash and pruritus (grade 1). No serious hypersensitivity reaction was reported and the subject recovered from the event.

In Study CT-P47 1.1 Part 2, TEAEs classified as hypersensitivity reactions were reported for 4 (2.8%) and 2 (1.4%) subjects in the CT-P47 and EU-RoActemra groups, respectively. All TEAEs were grade 1 in intensity. Reported PTs included myalgia, vascular headache, nausea and rash. No serious hypersensitivity reactions were reported and all of the subjects recovered from the event. There was no anaphylaxis identified according to Sampson criteria.

Study CT-P47 1.2

In Study CT-P47 1.2, a TEAE classified as a hypersensitivity reaction was reported for 1 (2.3%) subject in the US-Actemra group with signs and symptoms of chills, pyrexia and C-reactive protein (CRP) increased (grade 1). No serious hypersensitivity reaction was reported and the subject recovered from the event. There was no anaphylaxis identified according to Sampson criteria.

Study CT-P47 1.3

In Study CT-P47 1.3, TEAEs classified as hypersensitivity reactions were reported for 4 (2.6%) and 2 (1.3%) subjects in the CT-P47 AI and CT P47 PFS groups, respectively. All TEAEs were grade 1 or 2 in intensity. Reported PTs included urticaria, pruritis, pyrexia, vascular headache, nausea and vomiting. No serious hypersensitivity reactions were reported and all of the subjects recovered from the event. There was no anaphylaxis identified according to Sampson criteria.

Injection site reaction

Studies in RA patients

Study CT-P47 3.1

In Study CT-P47 3.1, injection site reaction was not assessed since the study drug was administered via IV infusion.

Study CT-P47 3.2

In Study CT-P47 3.2, TEAEs classified as injection site reaction were reported for 3 (9.1%) patients. All TEAEs were grade 1 or 2 in intensity. The most frequently reported sign and symptom of injection site reaction were injection site erythema and injection site pruritus (2 [6.1%] patients for each PT).

Healthy volunteer studies

Study CT-P47 1.1

In Study CT-P47 1.1 Part 1, TEAE classified as injection site reaction was reported for 1 (7.1%) subject in the CT-P47 group; signs and symptoms consisted of grade 1 injection site pain. The event was considered non-serious and the subject recovered from the event.

In Study CT-P47 1.1 Part 2, TEAEs classified as injection site reaction were reported for 4 (2.8%) and 5 (3.6%) subjects in the CT-P47 and EU-RoActemra groups, respectively. All TEAEs were grade 1 in

intensity. The most frequently reported sign and symptom of injection site reaction was injection site erythema (1 [0.7%] and 3 [2.1%] subjects, respectively). No serious injection site reactions were reported and all of the subjects recovered from the event.

Study CT-P47 1.2

In Study CT-P47 1.2, injection site reaction was not assessed since the study drug was administered via IV infusion.

Study CT-P47 1.3

In Study CT-P47 1.3, TEAEs classified as injection site reaction were reported for 14 (9.2%) and 5 (3.2%) subjects in the CT-P47 AI and CT P47 PFS groups, respectively. All TEAEs were grade 1 or 2 in intensity. The most frequently reported sign and symptom of injection site reaction was injection site erythema (10 [6.5%] and 3 [1.9%] subjects, respectively), followed by injection site swelling (5 [3.3%] and 1 [0.6%] subjects, respectively). No serious injection site reactions were reported and all of the subjects recovered from the event.

Hepatic events

Studies in RA patients

Study CT-P47 3.1

All TEAEs classified as hepatic event in Treatment Period I and II are summarised by PT for the Safety set in **Table 62** and **63**.

Table 62 Treatment-emergent adverse events classified as hepatic event by preferred term (treatment period I): safety set

System Organ Class Preferred Term	CT-P47 (N=234)	RoActemra (N=237)	Total (N=471)
	Number (%) of patients		
Total number TEAEs classified as hepatic event	**91**	**107**	**198**
Number of patients with at least 1 TEAE classified as hepatic event	**60 (25.6)**	**73 (30.8)**	**133 (28.2)**
Related to the study drug	35 (15.0)	46 (19.4)	81 (17.2)
Unrelated to the study drug	28 (12.0)	30 (12.7)	58 (12.3)
Hepatobiliary disorders	**13 (5.6)**	**7 (3.0)**	**20 (4.2)**

Abbreviation: TEAE, treatment-emergent adverse event.
Note: The total number of TEAEs included all patient events due to hepatic events. 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.
[a] Except for 1 event in each group, all TEAE of drug-induced liver injuries were due to methotrexate which was coadministered with study drug (reported terms: post-methotrexate liver injury/damage, methotrexate-induced liver injury). All drug-induced liver injuries were grade 1 in intensity except for 2 patients (1 patient in each group).

Table 63 Treatment-emergent adverse events classified as hepatic event by relationship and intensity (treatment period II): safety-treatment period II subset

System Organ Class Preferred Term Relationship	CT-P47 Maintenance (N=225)	RoActemra Maintenance (N=109)	Switched to CT-P47 (N=110)	Total (N=444)
	Number (%) of patients			
Total number TEAEs classified as hepatic event	**72**	**36**	**42**	**150**
Number of patients with at least 1 TEAE classified as hepatic event	**44 (19.6)**	**21 (19.3)**	**25 (22.7)**	**90 (20.3)**
Related to the study drug	34 (15.1)	17 (15.6)	22 (20)	73 (16.4)
Unrelated to the study drug	14 (6.2)	6 (5.5)	6 (5.5)	26 (5.9)
Hepatobiliary disorders	**5 (2.2)**	**2 (1.8)**	**2 (1.8)**	**9 (2.0)**
Drug-induced liver injury	3 (1.3)	1 (0.9)	0	4 (0.9)
Hepatic steatosis	1 (0.4)	0	0	1 (0.)
Hyperbilirubinaemia	1 (0.4)	0	2 (1.8)	3 (0.7)
Hypertransaminasaemia	0	1 (0.9)	0	1 (0.2)
Investigations	**41 (18.2)**	**19 (17.4)**	**24 (21.8)**	**84 (18.9)**
Alanine aminotransferase increased	30 (13.3)	13 (11.9)	15 (13.6)	58 (13.1)
Aspartate aminotransferase increased	14 (6.2)	8 (7.3)	9 (8.2)	31 (7.0)
Blood bilirubin increased	0	2 (1.8)	0	2 (0.5)
Transaminases increased	5 (2.2)	1 (0.9)	4 (3.6)	10 (2.3)
Gamma-glutamyltransferase increased	4 (1.8)	4 (3.7)	1 (0.9)	9 (2.0)
Hepatic enzyme increased	1 (0.4)	0	0	1 (0.2)
Hepatitis B DNA assay positive	0	0	1 (0.9)	1 (0.2)
Liver function test increased	2 (0.9)	1 (0.9)	3 (2.7)	6 (1.4)

Abbreviation: TEAE, treatment-emergent adverse event.
Note: The total number of TEAEs included all patient events due to hepatic events. 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.

Overall, 175 (37.2%) patients experienced at least 1 TEAE classified as hepatic event. The proportion of patients who experienced at least 1 TEAE classified as hepatic event was similar between CT-P47 and RoActemra groups (81 [34.6%] and 94 [39.7%], respectively), and among CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups. (78 [34.7%], 41 [37.6%], and 44 [40.0%] patients, respectively).

Importantly, except for 1 event in each group, all TEAEs of "drug-induced liver injury" (all reported during TP I) were due to methotrexate which was co-administered with study drug (reported terms: post-methotrexate liver injury/damage, methotrexate-induced liver injury). All drug-induced liver injuries were grade 1 in intensity except for 2 patients (1 patient in each group).

Study CT-P47 3.2

In Study CT-P47 3.2, a TEAE classified as a hepatic event was reported for 1 (3.0%) patient; this was a grade 2 event of alanine aminotransferase increased.

Healthy volunteer studies

Study CT-P47 1.1

In Study CT-P47 1.1 Part 1, there were no TEAEs classified as hepatic event.

In Study CT-P47 1.1 Part 2, TEAEs classified as hepatic events were reported for 4 (2.8%) and 5 (3.6%) subjects in the CT-P47 and EU-RoActemra groups, respectively. Most were grade 1 or 2 in intensity except for 2 subjects in the EU-RoActemra group. The reported TEAEs included alanine aminotransferase increased, aspartate aminotransferase increased and blood bilirubin increased. No serious hepatic events were reported, and all of the subjects recovered from the event.

Study CT-P47 1.2

In Study CT-P47 1.2, TEAEs classified as hepatic event were reported for 3 (6.7%), 3 (7.0%) and 2 (4.5%) subjects in the CT-P47, EU-RoActemra and US-Actemra groups, respectively. All TEAEs were grade 1 or 2 in intensity. The most frequently reported TEAE was alanine aminotransferase increased (2 [4.4%], 1 [2.3%] and 1 [2.3%] subjects, respectively), followed by blood bilirubin increased (2 [4.7%] and 1 [2.3%] subjects in the EU-RoActemra and US-Actemra groups, respectively). No serious hepatic events were reported, and all of the subjects recovered or were recovering from the event.

Study CT-P47 1.3

In Study CT-P47 1.3, TEAEs classified as hepatic event were reported for 4 (2.6%) and 4 (2.5%) subjects in the CT-P47 AI and CT-P47 PFS groups, respectively. All TEAEs were grade 1 or 2 in intensity. The most frequently reported TEAE was alanine aminotransferase increased (4 [2.6%] and 2 [1.3%] subjects, respectively). No serious hepatic events were reported, and all of the subjects recovered from the event.

Haemorrhage

Studies in RA patients

Study CT-P47 3.1

Overall, 13/471 (2.8%) patients experienced at least 1 TEAE classified as haemorrhage. The proportion of patients who experienced at least 1 TEAE classified as haemorrhage was similar between CT-P47

and RoActemra groups (4/234 [1.7%] and 9/237 [3.8%], respectively), and among CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups (4/225 [1.8%], 4/109 [3.7%], and 5/110 [4.5%] patients, respectively).

Overall, all TEAEs classified as haemorrhage were grade 1 or 2 in intensity except for 1 (0.4%) patient who experienced a grade 3 TEAE of uterine haemorrhage in the Switched to CT-P47 group during Treatment Period II. Except for this event, all haemorrhages were considered as not medically significant bleeding events. The most frequently reported TEAE classified as haemorrhage was contusion (2/234 (0.9%) and 4/237 (2.5%) in the CT-P47 and RoActemra groups during TP I and 2/235 (0.9%), 4/109 (3.7%) and 2/110 (1.8%) patients during TP II in the CT P47 maintenance, EU-RoActemra maintenance and Switched to CT-P47 groups, respectively). Other reported PTs, mostly reported as single events, included genital haemorrhage, epistaxis, haemoptysis, ecchymosis and haematoma.

Except for one event of genital haemorrhage, all haemorrhage events were considered unrelated to study drug.

Study CT-P47 3.2

In Study CT-P47 3.2, there were no TEAEs classified as haemorrhage.

Healthy volunteer studies

Study CT-P47 1.1

In Study CT-P47 1.1 Part 1, there were no TEAEs classified as haemorrhage.

In Study CT-P47 1.1 Part 2, TEAEs classified as haemorrhage were reported for 2 (1.4%) subjects in the CT-P47 group only. All of TEAEs were grade 1 in intensity. No serious haemorrhages were reported, and all events were considered as medically not clinically significant bleeding events. All of the subjects recovered from the event.

Study CT-P47 1.2

In Study CT-P47 1.2, a TEAE classified as haemorrhage was reported for 1 (2.3%) subject in the EU-RoActemra group. This was a grade 1 contusion considered unrelated to study drug. The event was considered as a medically not clinically significant bleeding event, and the subject recovered from the event.

Study CT-P47 1.3

In Study CT-P47 1.3, TEAEs classified as haemorrhage were reported for 2 (1.3%) and 3 (1.9%) subjects in the CT-P47 AI and CT-P47 PFS groups, respectively. All TEAEs were grade 1 in intensity. The reported PTs included puncture site bruise, injection site haemorrhage, epistaxis and haemoptysis. No serious haemorrhages were reported, and all events were considered as medically not clinically significant bleeding events. All of the subjects recovered from the event without treatment.

Gastrointestinal perforation

There were two events of gastrointestinal perforation in study CT-P47 3.1, both reported by the applicant to have occurred in the CT-P47 group (TP I) and in the CT-P47 Maintenance group (TP II) group; however as the total number is reported to be 2 events, obviously each event continued from TP I to TP II. One event was Grade 2. However, the other TEAE was gastrointestinal perforation classified as grade 5 unrelated peritonitis. There were no TEAEs classified as a gastrointestinal perforation in any of the other studies.

Malignancy

Overall, 1/237 (0.4%) patient in the EU-RoActemra group experienced a TEAE classified as malignancy (grade 3 unrelated pancreatic neoplasm) during Treatment Period I in Study CT-P47 3.1. There were no TEAEs classified as a malignancy in any of the other studies.

Demyelinating disorder

No TEAEs classified as a demyelinating disorder were reported in any studies.

2.6.8.4. Laboratory findings

Studies in RA patients

In Study CT-P47 3.1, the majority of laboratory parameters had no CTCAE grade (i.e., the post-baseline laboratory result did not satisfy any CTCAE grade criteria) or were CTCAE grade 1 or 2.

In general, there was no notable difference among all groups for patients with any grade of CTCAE in laboratory parameters (**Table 64**).

The most frequently reported CTCAE grade 3 or higher laboratory parameter as most severe during Overall Period was neutrophil count decreased; grade 3 neutrophil count decreased was reported for 33 (7.0%) patients (14 [6.0%] and 19 [8.0%] patients in the CT-P47 and RoActemra groups, respectively, and 14 [6.2%], 9 [8.3%], and 10 [9.1%] patients in the CTP47 maintenance, RoActemra maintenance, and switched to CT-P47 groups, respectively) and grade 4 neutrophil count decreased was reported for 3 (0.6%) patients (2 [0.9%] and 1 [0.4%] patients in the CT-P47 and RoActemra groups, respectively, and none in the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups).

Table 64 Laboratory parameters of most severe CTCAE grading (grade 3 or higher) recorded post-baseline (overall period): safety set

	Initial Randomization		2nd Randomization		
Laboratory CTCAE Term	CT-P47 (N=234)	RoActemra (N=237)	CT-P47 Maintenance (N=225)	RoActemra Maintenance (N=109)	Switched to CT-P47 (N=110)
Grade	Number (%) of patients				
Chemistry					
ALT increased					
Grade 3	4 (1.7)	4 (1.7)	3 (1.3)	1 (0.9)	0
AST increased					
Grade 3	2 (0.9)	0	2 (0.9)	0	0
Blood bilirubin increased					
Grade 3	0	2 (0.8)	0	2 (1.8)	0
CPK increased					
Grade 3	1 (0.4)	1 (0.4)	1 (0.4)	0	1 (0.9)
Grade 4	1 (0.4)	1 (0.4)	1 (0.4)	0	1 (0.9)
Cholesterol high					
Grade 3	1 (0.4)	2 (0.8)	1 (0.4)	1 (0.9)	1 (0.9)
GGT increased					
Grade 3	3 (1.3)	2 (0.8)	3 (1.3)	1 (0.9)	1 (0.9)
Hyperkalemia					
Grade 3	0	1 (0.4)	0	1 (0.9)	0

Table 64 continued Laboratory parameters of most severe CTCAE grading (grade 3 or higher) recorded post-baseline (overall period): safety set

Laboratory CTCAE Term	Initial Randomization		2nd Randomization		
	CT-P47 (N=234)	RoActemra (N=237)	CT-P47 Maintenance (N=225)	RoActemra Maintenance (N=109)	Switched to CT-P47 (N=110)
Grade	Number (%) of patients				
Hypertriglyceridemia					
Grade 3	5 (2.1)	5 (2.1)	5 (2.2)	2 (1.8)	3 (2.7)
Grade 4	2 (0.9)	0	2 (0.9)	0	0
Hypocalcemia					
Grade 3	1 (0.4)	0	1 (0.4)	0	0
Hypoglycemia					
Grade 3	1 (0.4)	0	1 (0.4)	0	0
Hypokalemia					
Grade 3	1 (0.4)	0	1 (0.4)	0	0
Hyponatremia					
Grade 3	0	1 (0.4)	0	1 (0.9)	0
Hematology					
Lymphocyte count decreased					
Grade 3	1 (0.4)	3 (1.3)	1 (0.4)	1 (0.9)	2 (1.8)
Neutrophil count decreased					
Grade 3	14 (6.0)	19 (8.0)	14 (6.2)	9 (8.3)	10 (9.1)
Grade 4	2 (0.9)	1 (0.4)	0	0	0
Platelet count decreased					
Grade 3	0	1 (0.4)	0	1 (0.9)	0
White blood cell decreased					
Grade 3	1 (0.4)	2 (0.8)	0	0	1 (0.9)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CTCAE, Common Terminology Criteria for Adverse Events; GGT, Gamma glutamyl transpeptidase.
Note: The number and percentage were summarised using the most severe grade. If a patient's most extreme post-baseline value fails to satisfy any CTCAE criteria, the result is classified as 'No Grade'.

In Study CT-P47 3.2, the majority of laboratory parameters had no CTCAE grade or were CTCAE grade 1 or 2. Grade 3 laboratory parameters included neutrophil count decreased (2 [6.1%] patients) and white blood cell decreased (1 [3.0%] patient).

Healthy volunteer studies

In Study CT-P47 1.1, the majority of laboratory parameters had no or low CTCAE grade (grade 1 or 2). The most frequently reported CTCAE grade 3 laboratory parameter was neutrophil count decreased. In Part 1, 2 (6.9%) subjects (1 [7.1%] and 1 [6.7%] subjects in the CT-P47 and EU-RoActemra groups, respectively) had grade 3 neutrophil count decreased. In Part 2, 33 (11.6%) subjects (12 [8.3%] and 21 [15.0%] subjects, respectively) had grade 3 neutrophil count decreased.

In Study CT-P47 1.1 Part 1, 1 (6.7%) subject in the EU-RoActemra group was reported with grade 4 neutrophil count decreased and 1 (6.7%) subject in the EU-RoActemra group was reported with grade 4 hypertriglyceridemia. In Part 2, the most frequently reported CTCAE grade 4 laboratory parameter was CPK increased in 7 (2.5%) subjects (5 [3.5%] and 2 [1.4%] subjects in the CT-P47 and EU RoActemra groups, respectively).

Also in Study CT-P47 1.2, the majority of the laboratory parameters had no or low CTCAE grade (grade 1 or 2). The most frequently reported CTCAE grade 3 or 4 laboratory parameter was neutrophil count decreased for 15 (33.3%), 13 (30.2%) and 12 (27.3%) subjects in the CT-P47, EU-RoActemra and US-Actemra groups, respectively.

Lastly, in Study CT-P47 1.3, the majority of the laboratory parameters also had no or low CTCAE grade (grade 1 or 2). The most frequently reported CTCAE grade 3 or 4 laboratory parameter was neutrophil count decreased for 22 (14.4%) and 11 (7.0%) subjects in the CT-P47 AI and CT P47 PFS groups, respectively.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Not applicable.

2.6.8.7. Immunological events

See section 2.6.2 Clinical Pharmacology for data related to immunogenicity.

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

Not applicable for biosimilars.

2.6.8.9. Discontinuation due to adverse events

Studies in RA patients

For Study CT-P47 3.1, all TEAEs leading to study drug discontinuation are summarised by SOC and PT for the Safety Set (Overall Period and Treatment Period I) and the Safety–Treatment Period II subset (Treatment Period II) in **Table 63**.

Treatment-emergent AEs leading to discontinuation of study drug were reported for 13/234 (5.6%) and 20/237 (8.4%) patients in the CT-P47 and RoActemra groups, respectively, and 10/225 (4.4%), 5/109 (4.6%), and 4/110 (3.6%) patients in the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups, respectively (**Table 65**).

TEAEs leading to study drug discontinuation considered by the investigator to be related to the study drug were reported for 8 (3.4%) and 16 (6.8%) patients in the CT-P47 and RoActemra groups, respectively, and 5 (2.2%), 3 (2.8%), and 4 (3.6%) patients in the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups, respectively.

No relevant differences were observed between study groups in the number or reason for discontinuation of study drug. Most common TEAEs leading to study drug discontinuation were

Investigations (total 11, related 10; most common PT ALT increased [total 7, related 6]); hypersensitivity (total 4, related 4); neutropenia (total 3, related 3), infections (total 5, related 3), and Skin and subcutaneous tissue disorders (total 3, related 3; incl. dermatitis, erythema nodosum, and urticaria). (Tabulated data on PTs leading to discontinuation not included for brevity).

Table 65 Treatment-emergent adverse events (TEAEs) leading to study drug discontinuation. safety set (overall period)

System Organ Class [1] Preferred Term [1]	CT-P47 (N=234)	CT-P47 Maintenance (N=225)	RoActemra (N=237)	RoActemra Maintenance (N=109)	Switched to CT-P47 (N=110)	Total (N=471)
Total Number of TEAEs Leading to Study Drug Discontinuation	13	10	22	5	4	35
Number of Patients With at Least One TEAE Leading to Study Drug Discontinuation	13 (5.6%)	10 (4.4%)	20 (8.4%)	5 (4.6%)	4 (3.6%)	33 (7.0%)
Grade 1	1 (0.4%)	1 (0.4%)	0	0	0	1 (0.2%)
Grade 2	7 (3.0%)	6 (2.7%)	9 (3.8%)	2 (1.8%)	2 (1.8%)	16 (3.4%)
Grade 3	3 (1.3%)	2 (0.9%)	9 (3.8%)	2 (1.8%)	2 (1.8%)	12 (2.5%)
Grade 4	1 (0.4%)	0	2 (0.8%)	1 (0.9%)	0	3 (0.6%)
Grade 5	1 (0.4%)	1 (0.4%)	0	0	0	1 (0.2%)
Related	8 (3.4%)	5 (2.2%)	16 (6.8%)	3 (2.8%)	4 (3.6%)	24 (5.1%)
Grade 1	1 (0.4%)	1 (0.4%)	0	0	0	1 (0.2%)
Grade 2	4 (1.7%)	3 (1.3%)	8 (3.4%)	2 (1.8%)	2 (1.8%)	12 (2.5%)
Grade 3	2 (0.9%)	1 (0.4%)	6 (2.5%)	0	2 (1.8%)	8 (1.7%)
Grade 4	1 (0.4%)	0	2 (0.8%)	1 (0.9%)	0	3 (0.6%)
Unrelated	5 (2.1%)	5 (2.2%)	4 (1.7%)	2 (1.8%)	0	9 (1.9%)
Grade 2	3 (1.3%)	3 (1.3%)	1 (0.4%)	0	0	4 (0.8%)
Grade 3	1 (0.4%)	1 (0.4%)	3 (1.3%)	2 (1.8%)	0	4 (0.8%)
Grade 5	1 (0.4%)	1 (0.4%)	0	0	0	1 (0.2%)

Note: At each level of summarisation, patients are counted once if they reported one or more events. Only the most severe event is counted. The event is considered to be related if the relationship is defined as ‘Possible’, ‘Probable’, ‘Definite’. The intensity is defined as Grade 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Life-threatening, 5 = Death.

In Study CT-P47 3.2, a TEAE leading to study drug discontinuation was reported for 2 (6.1%) patients. The respective PTs were grade 1 Erythema and grade 3 Cerebrovascular disorder, and both events were considered to be related to study drug by the investigator.

Healthy volunteer studies

Not relevant, as all studies were single dose studies.

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

The applicant has developed CT-P47 as a proposed biosimilar to RoActemra (tocilizumab). The clinical development programme for CT-P47 includes 1 comparative efficacy and safety study in patients with moderate to severe active rheumatoid arthritis (RA) (Study CT-P47 3.1), 1 completed auto-injector (AI) usability study in patients with moderate to severe active RA (Study CT-P47 3.2) and 3 completed Phase 1 clinical studies in healthy subjects (Studies CT-P47 1.1, CT-P47 1.2 and CT-P47 1.3). Safety assessments included monitoring and recording of adverse events, vital signs monitoring (including systolic and diastolic BP, heart rate, respiratory rate and body temperature), comprehensive clinical laboratory testing and assessment of immunogenicity.

The safety evaluations were planned according to the known safety profile of tocilizumab, considering the adverse reactions presented in the SmPC and other available clinical information. The safety analyses were performed on the safety analysis sets, consisting of all subjects receiving at least 1 dose of study drug. Within the application documentation, the safety data has been presented by individual study and has not been pooled; in light of the different study populations and routes of administration, this is deemed acceptable. Overall, the applicant's approach to the safety analyses is endorsed by the CHMP.

A total of 513 healthy volunteers were exposed to a single dose of CT-P47 in the PK studies. In addition, 234 RA patients in Study CT-P47 3.1 and 33 patients in Study CT-P47 3.2 received at least one dose of CT-P47, with additional patients exposed in Study CT-P47 3.1 after the switch at Week 24.

Overall, the adverse event profiles of CT-P47 and EU-RoActemra in terms of nature, frequency and severity were quite comparable in the clinical RA studies; a higher number of infection-related AEs was however seen for CT-P47 in Study CT-P47 3.1, and this observation is discussed in the section on AESIs further below. In the RA study CT-P41 3.1, both products seemed to be generally reasonably well tolerated, with most reported AEs being grade 1 or 2. No unexpected clustering of events was seen, and the overall profile for both products seemed consistent with expectations based on the known profile of tocilizumab. Local tolerability of the intravenous formulation appears to have been acceptable, as infusion site reactions were not reported as TEAEs in Study 3.1.

As in the RA studies, the overall AE profiles were comparable between CT-P47 and EU-RoActemra in the healthy volunteer studies. A high proportion of the reported AEs were injection site reactions (in SC studies) and laboratory abnormalities, which is not in itself unexpected. In contrast to the RA study 3.1 in which a higher frequency of infections was reported with CT-P47, the proportion was higher for EU-RoActemra in the SC study 1.1. In Study 1.3, a higher proportion of subjects developed injection site reactions in the AI group compared to the PFS group. The applicant ascribes this to differences in the administration technique, and as all events were grade 1 or 2 and of a transient nature, the phenomenon does not appear clinically concerning.

In Study CT-P47 3.1, the frequency of infections was substantially higher in the CT-P47 group compared to the EU-RoActemra group during Treatment Period I: the corresponding percentages were 47.0% for CT-P47 and 35.4% for EU-RoActemra. The observed difference in incidence of infections during TP I was mostly due to a higher incidence of upper respiratory infections (URTIs) in the CT-P47 group. URTIs are a known adverse reaction of tocilizumab. During TP II of the study, there was no difference in the overall incidence of infections between the CT-P47 maintenance, RoActemra maintenance, and Switched to CT-P47 groups, therefore, the difference noted in TP I is deemed to be likely due to chance.

There was a numerical imbalance in cases with latent tuberculosis during TP II, with more cases in the CT-P47 maintenance group (N=16/225, 7.1%) vs. the RoActemra Maintenance group (N=3/109, 2.8%) and the Switched to CT-P47 group (N=5/110, 4.5%). No cases were reported during TP I, since after baseline, IGRA was only measured at Week 24, and the results were reported for TP II. It is unclear why the IGRA test was not repeated near to study initiation for those who were IGRA positive at screening and why these subjects did apparently not undergo chest X-ray for diagnosis of latent TB. When considering only events that were deemed to be related to the study drug, the gap was smaller but did not disappear. Potential underlying reasons for this difference were upon request scrutinised by the applicant, but no clear explanation for the difference was identified. However, none of the patients experienced active TB or signs and symptoms of TB, therefore, the difference in latent TB cases between the study groups is not deemed to affect safety of CT-P47. Therefore, the issue on initial diagnosis of latent TB was not pursued further.

Apart from the infectious AEs discussed above, analyses of data regarding the other pre-specified AESI demonstrate comparable profiles between CT-P47 and EU-RoActemra. It is acknowledged that some of the AESI are rare events, and consequently, the discriminatory power of the programme to detect differences in rare events is low. Overall, no concerns are currently raised.

Serious adverse events were overall infrequent, and the nature, severity and frequency of events was comparable between the treatment groups. Most events were single occurrences, with no clustering discernible.

Discontinuations were also overall infrequent. Overall, 96.2% and 92.4% of subjects in the CT-P47 and RoActemra groups, respectively, completed TP I. TP 2 was completed by 93.3%, 91.7% and 92.7% of the CT-P47 Maintenance, RoActemra Maintenance, and Switched to CT-P 47 groups, respectively. There were no relevant differences in the reasons for discontinuation of the study or discontinuation of study drug between study groups.

The frequency of grade 3 or higher laboratory abnormalities was low, and reported abnormalities were consistent with the known safety profile of tocilizumab. No concerning differences between CT-P47 and EU-RoActemra were seen.

A lower rate of ADA formation was noted with IV administration as compared to SC administration. The apparently low immunogenicity in RA patients could also be partly related to concurrent use of MTX. However, across all studies, the frequencies of ADA and NAb formation were comparable between the CT-P47 and EU-RoActemra groups.

The development of ADAs did not seem to have any effect on safety. Among healthy volunteers with the highest ADA titres, no AEs were reported. In RA patients, hypersensitivity reactions were overall proportionally more frequent in the ADA-positive subgroup in both treatment groups, but the very small proportion of ADA-positive patients does not allow further conclusions. Overall, no concerns regarding biosimilarity are raised as regards frequencies of ADA and NAb formation or effect of ADA/NAbs on safety.

2.6.10. Conclusions on the clinical safety

Comprehensive analyses of safety data from the CT-P47 development programme have been provided for assessment. The size of the safety database is considered sufficient to enable a reasonable analysis of comparability between CT-P47 and EU-RoActemra.

The data submitted is considered to support biosimilarity of CT-P47 and EU-RoActemra from the safety perspective.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 66 Safety concerns

Summary of safety concerns	
Important identified risks	Serious infection * Complications of diverticulitis * Neutropenia Hepatotoxicity
Important potential risks	Thrombocytopenia and the potential risk of bleeding Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events Malignancies Demyelinating disorders Immunogenicity
Missing information	None

* The safety concerns "serious infection" and "complications of diverticulitis" are considered important identified risks for chronic tocilizumab dosing, but are assessed as important potential risks for the indication of COVID-19.

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Table 67 Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious Infections*	Routine risk minimisation measures: SmPC sections 4.3, 4,4, and 4.8 PIL sections 2 and 4. Legal status: Prescription only medicine Additional risk minimisation measures: Patient Alert Card Patient Brochure Healthcare Provider Brochure Dosing Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Complications of Diverticulitis*	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PIL sections 2 and 4. Legal status: Prescription only medicine Additional risk minimisation measures: Patient Alert Card Patient Brochure Healthcare Provider Brochure Dosing Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Neutropenia	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8 PIL section 4. Legal status: Prescription only medicine Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Patient Brochure Healthcare Provider Brochure Dosing Guide	
Hepatotoxicity	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8 PIL sections 2 and 4. Legal status: Prescription only medicine Additional risk minimisation measures: Patient Alert Card Patient Brochure Healthcare Provider Brochure	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Thrombocytopenia and the potential risk of bleeding	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8 Legal status: Prescription only medicine Additional risk minimisation measures: Patient Brochure Healthcare Provider Brochure	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Elevated Lipid Levels and Potential Risk of Cardiovascular /Cerebrovascular Events	Routine risk minimisation measures: SmPC sections 4.4, and 4.8 PIL sections 2 and 4. Legal status: Prescription only medicine Additional risk minimisation measures: Patient Brochure Healthcare Provider Brochure Dosing Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Malignancies	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PIL section 2. Legal status: Prescription only medicine Additional risk minimisation measures: Patient Brochure Healthcare Provider Brochure Dosing Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Demyelinating Disorders	Routine risk minimisation measures: SmPC section 4.4 Legal status: Prescription only medicine Additional risk minimisation measures: Healthcare Provider Brochure	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimisation measures: SmPC section 4.8 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 safety concerns "serious infection" and "complications of diverticulitis" are considered important identified risks for chronic tocilizumab dosing, but are assessed as important potential risks for the indication of COVID-19.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of two bridging reports.

Avtozma 20 mg/ml concentrate for solution for infusion (daughter) was compared with RoActemra 20 mg/mL concentrate for solution for infusion (EMEA/H/C/000955 – IB/0122/G) for contents of the PL including key safety messages and with Herzuma 150 mg powder for concentrate for solution for infusion trastuzumab (EMEA/H/C/002575/0000) for design/layout/format.

Avtozma 162 mg solution for injection in pre-filled syringe with safety guard / in pre-filled pen was compared with RoActemra 162 mg solution for injection in pre-filled syringe / in pre-filled pen (EMEA/H/C/000955 – IB/0122/G) for contents of the PL including key safety messages and Remsima 120 mg solution for injection in pre-filled syringe / in pre-filled pen (EMEA/H/C/002576/X/0062) for design/layout/format.

The bridging reports submitted by the applicant have been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Avtozma (Tocilizumab) is included in the additional monitoring list as it is a biological product that does not contain a new active substance and is authorised after 1 January 2011.

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

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

CT-P47 is being developed as a biosimilar candidate to EU-approved RoActemra (tocilizumab). The proposed indications for CT-P47 are the same as those approved for EU RoActemra:

Avtozma, in combination with methotrexate (MTX), is indicated for:

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma 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.

Avtozma is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. *(Only the concentrate for solution for infusion)*

Avtozma is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older (*concentrate for solution for infusion*)/ 1 years of age and older (*solution for injection in prefilled syringe*)/ 12 years of age and older (*solution for injection in pre-filled pen*) who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Avtozma can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Avtozma in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older (*concentrate for solution for infusion* and *solution for injection in prefilled syringe)/* 12 years of age and older *(solution for injection in pre-filled pen)*, who have responded inadequately to previous therapy with MTX. Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older. *(Only the concentrate for solution for infusion)*

Avtozma is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients. *(Only the solution for injection in prefilled syringe and in prefilled pen)*

Quality program

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. Received CHMP scientific advices have been mostly followed in the presented similarity exercise.

Both CT-P47 and EU-RoActemra are provided in SC (PFS, 180 mg/mL) and IV (vial, 20 mg/mL) presentations with slightly different formulations. A 2-way analytical comparability study was

performed separately for SC and IV presentations, including several independent CT-P47 SC/IV batches and EU-RoActemra SC/IV batches.

A comprehensive set of state-of-the-art orthogonal methods was used to compare the primary and higher order structures, post-translational modifications, charged variants, glycan structures, purity and impurities, protein concentration, and biological activity of Fab and Fc related functions. Biological assays include soluble and cell membrane IL-6 receptor binding, IL-6 mediated cell proliferation, and inhibition of IL-6 mediated intracellular signal transduction. Additional characterisation studies, including e.g. demonstration of lack of ADCC and CDC activity and comparison of forced degradation profiles were performed on reduced number of batches. When differences were observed, the potential impact of these on safety, efficacy, PK or immunogenicity was discussed. Overall, the presented approach for demonstrating biosimilarity is considered appropriate.

Non-clinical program

The nonclinical comparative assessment included a battery of *in vitro* functional activity studies, which were identical and presented under the Quality data. In addition, a GLP-compliant month of duration repeated-dose toxicology and toxicokinetic study was conducted in cynomolgus monkeys.

Clinical program

The clinical development program supporting the biosimilarity of CT-P47 to the reference product EU-RoActemra and US-Actemra consisted of two pivotal PK-studies comparing the SC and IV administration of CT-P47 to the EU-originator RoActemra and one Phase 3 efficacy and safety study with patients with moderate to severe RA comparing IV administration of CT-P47 to the EU-originator RoActemra. In the Phase 3 trial, during Treatment Period 1 (weeks 0 to 24), subjects were randomised to receive either CT-P47 or EU-RoActemra. Prior to dosing at Week 24, patients in the RoActemra treatment were randomly assigned in a ratio of 1:1 to either continue with RoActemra or undergo transition to CT-P47 for Treatment Period II. All patients initially assigned to CT-P47 treatment group at Day 1 (Week 0) continued their treatment with CT-P47 until Week 48. A second randomisation process was conducted to all subjects to maintain the study blind. In addition, to support the autoinjector (AI) presentation, a PK bioequivalence study in healthy volunteers was conducted comparing SC administration with AI vs. SC administration with pre-filled syringe (PFS), which has been used to demonstrate the PK biosimilarity with the originator product. Furthermore, a single-arm, open-label, multiple-dose, phase 3 study was conducted to evaluate usability of the AI in adult patients with RA.

The safety profiles of CT-P47 and the reference product were assessed in the clinical PK studies as well as the clinical RA study through comparative, descriptive analyses of adverse events, laboratory data and immunogenic potential. For all clinical studies, the safety analyses were performed on the safety analysis sets which included all randomised subjects who received any investigational product.

The clinical development generally followed the applicable guidelines Guideline on similar biological medicinal products (EMEA/CHMP/42832/2005 Rev. 1) and Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies - Non-Clinical and Clinical Issues (EMA/CHMP/BMWP/403543/2010).

3.2. Results supporting biosimilarity

Quality

Similarity between CT-P47 and EU-RoActemra has been demonstrated for the following physicochemical and biological properties:

- Primary structure and post-translational modifications
- Charged variants
- Glycosylation
- Purity/impurity
- Higher order structure
- Content (protein concentration)
- Thermal stability and degradation studies
- Biological activity:
  - sIL-6R binding
  - mIL-6R binding
  - Inhibition of IL-6 mediated cell proliferation
  - Competition of IL-6 and tocilizumab binding to IL-6R
  - Dissociation of IL-6 from IL-6/sIL-6R complex by tocilizumab
  - Inhibitory activity on IL-6 induced JAK-STAT pathway
  - C1q Binding
  - FcγRIIa, FcγRIIb, and FcγRIa binding
  - FcRn binding
  - Lack of ADCC and CDC activity

For further details see Table 1 Summary of biosimilarity assessment in the Quality section above.

Nonclinical

The comparative *in vitro* functional data of CT-P47 and EU-RoActemra demonstrated similar Fab-related activities in the binding to soluble and membrane bound IL-6R, inhibition of IL-6-mediated cell proliferation, competition of IL-6 and tocilizumab binding to IL-6R, and dissociation of IL-6 from IL-6/sIL-6R complex by tocilizumab. In addition, CT-P47 and EU-RoActemra showed comparable Fc-related activities in binding to C1q and Fcγ receptors I, IIa, and IIb, and lack of ADCC and CDC activities.

The supportive repeated dose toxicology study in cynomolgus monkeys did not reveal significant differences between CT-P47 and EU-RoActemra in the pharmacokinetic and toxicology characteristics.

Clinical

Pharmacokinetics

Two pivotal phase 1 PK studies were conducted in healthy volunteers to support the PK similarity of CT-P47 with EU-RoActemra after SC and IV administration.

The PK equivalence study CT-P47 1.1 comparing a single SC 162 mg dose of CT-P47 to EU-RoActemra showed that the 90% for GM ratio of the three primary PK endpoints, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max}, were within the predefined conventional equivalence margins of 80.00 to 125.00% indicating similarity of CT-P47 with EU-RoActemra. The secondary parameters (T_{max}, $t_{1/2}$, $\%AUC_{ext}$, λ_z, CL, and V_z) were comparable between the treatments.

After intravenous infusion of a single 8 mg/kg dose in healthy volunteers (study CT-P47 1.2), CT-P47 was confirmed as similar with EU-RoActemra as the 90% CIs for GM ratio of all the three primary PK parameters $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max} were within the conventional equivalence margins 80.00% to 125.00%. The secondary parameters (T_{max}, $t_{1/2}$, $\%AUC_{ext}$, λ_z, CL, and V_z) were comparable between the treatments. Moreover, the study showed PK similarity between CT-P47 and US-Actemra as well as between EU-RoActemra and US-Actemra.

In the phase 3 study CT-P47 3.1, the observed tocilizumab C_{trough} concentrations (mean ± SD) on Week 20 were 14.8 µg/ml ± 11.2 µg/ml for CT-P47 and 15.7 µg/ml ± 11.3 µg/ml for RoActemra being well in line with the concentrations previously reported for the reference product. Switching RoActemra treatment to CT-P47 did not have significant effect on the tocilizumab concentrations as the C_{trough} were generally comparable between CT-P47 maintenance, RoActemra maintenance, and switched CT-P47 groups up to week 52 treatment.

PK of CT-P47 AI and CT-P47 PFS were compared in healthy subjects to establish a bridge to clinical data conducted with the PFS. Comparing SC administration of CT-P47 with AI or PFS, the geometric LSM ratio (90% CI) for C_{max} were 90.25% (82.98; 98.16) and for $AUC_{0\text{-}inf}$ were 94.02% (85.87, 102.94) for CT-P47 AI versus CT-P47 PFS, thus, indicating PK similarity between CT-P47 AI and CT-P47 PFS. The secondary PK parameters were comparable between the treatment groups supporting the similar exposure for both administration devices. An additional statistical analysis and 90% CI for geometric LSM T/R ratio of $AUC_{0\text{-}last}$ confirmed the similarity of the extent of exposure between SC CT-P47 administered with AI and PFS as 90% CI was within the equivalence limits of 80.00% to 125.00%.

Pharmacodynamics

Soluble interleukin-6 receptor (sIL-6R) concentrations were collected for assessment of tocilizumab effect in the phase 3 study CT-P47 3.1. Similar changes in descriptively reported levels of sIL-6R were seen over the course of the study in all study groups.

No relevant differences were observed in immunogenicity of CT-P47 and EU-RoActemra in study CT-P47 3.1. Conversion to ADA and NAb positivity was low. Exposure to tocilizumab was similarly affected by ADA during treatment with CT-P47 and RoActemra. Immunogenicity had no obvious impact on safety in any study group.

Clinical efficacy

The primary objective of the pivotal study CT-P47 3.1 was to demonstrate that CT-P47 is equivalent to EU-RoActemra in terms of efficacy as determined by clinical response according to the change from baseline in disease activity measured by DAS28 (Erythrocyte-Sedimentation Rate [ESR]) at Week 12 in adult male or female patients with moderate to severe RA. Assignment to CT-P47 and a stable dose of methotrexate, regardless of discontinuation and use of additional medications, was compared to assignment to EU-RoActemra and a stable dose of methotrexate, regardless of discontinuation and use of additional medications. The primary population of primary endpoint was the intention-to-treat (ITT) Set evaluated under a treatment policy estimand.

Results on the primary endpoint/primary estimand were comparable between the study groups during Treatment Period I: the absolute mean change of DAS28(ESR) at Week 12 was -3.01 (SE 0.121) for CT-P47 and -3.00 (0.120) for EU-RoActemra. This corresponded to an LS mean difference of 0.01 with a 95% CI of (-0.26, 0.24). The 95% CIs for the LS mean differences in change from baseline between groups were fully included within the respective predefined equivalence intervals (-0.6 to 0.6). The mean change of DAS28(ESR) in both treatment groups was considered high and clinically relevant. A supportive analysis for the primary efficacy endpoint conducted using the per-protocol (PP) Set gave

comparable results between the study groups. In addition, a sensitivity analysis to evaluate the impact of missing data was conducted on ITT Set and yielded comparable results between the study groups.

Secondary efficacy endpoints included: ACR20, ACR50 and ACR70; individual components of the ACR; hybrid ACR response, DAS28 (CRP); DAS28 (ESR) (other time points except for Week 12); individual components of the DAS28; EULAR response; Simplified disease activity index (SDAI) and clinical disease activity index (CDAI); ACR/EULAR remission (Boolean-based definition); 36-item short form health survey (SF-36) and Joint damage progression based on radiographic evaluations. Secondary endpoints were followed for the duration of the study and reported descriptively. No multiplicity control was implemented for secondary endpoints.

Available results for all secondary endpoints were overall comparable between the CTP47 and EU-RoActemra groups during Treatment Period I. At Week 24, the change from baseline in DAS28(ESR) [mean(SD)] was for the CT-P47 and EU-RoActemra groups -3.858 (1.2402) and -3.720 (1.3945), respectively. At Week 24, the patients were re-randomised for Treatment Period II. Overall, results of all secondary efficacy endpoints were comparable for the CT-P47 vs. EU-RoActemra vs. the switch group (from EU-Roactemra to CT-P47) during Treatment Period II. The mean actual values and change from baseline of DAS28 (ESR) and DAS28 (CRP) were similar between study groups throughout the study. The proportion of patients achieving clinical response according to the ACR20, ACR50, and ACR70 criteria was similar between the two groups in Treatment Period I and the three groups in Treatment Period II. Sustained efficacy to comparable extent was achieved also in other secondary efficacy endpoints in the Switched to CT-P47 group as well as the CT-P47 and EU-RoActemra maintenance groups during Treatment Period II up to Week 52 (end of study). The mean increase from baseline in total sharp radiographic joint damage scores was generally similar among the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups in the ITT maintenance set. At end of the study (Week 52), around 1/3 of subjects had achieved ACR/EULAR remission (Boolean-based definition): 32.4%, 32.1% and 37.3% in the CT-P47, RoActemra Maintenance and Switched to CT-P47 groups, respectively. PP set analyses were performed as supportive analyses and yielded largely similar results to that of the main analysis.

Clinical safety

The analysis of currently available adverse event data and laboratory data generally support the view that the safety profiles of CT-P47 and EU-RoActemra could be comparable:

- In the clinical RA study CT-P47 3.1
    - *During Treatment Period I*,
        - 1014 TEAEs were reported in 375 (79.6%) patients with a similar proportion of patients experiencing TEAEs between the 2 groups (188 [80.3%] patients in the CT-P47 group and 187 [78.9%] patients in the RoActemra group).
        - The most frequently reported TEAEs by PT were upper respiratory tract infection (50 [21%] and 40 [17%] patients, respectively), followed by alanine aminotransferase increased (37 [16%] and 48 [20%] patients, respectively), leukopenia (20 [9%] and 25 [11%] patients, respectively) and neutropenia (19 [8%] and 23 [10%] patients, respectively).
        - Out of all events, TEAEs in 232 (49.3%) patients were considered by the investigator to be related to the study drug, with a similar proportion in each group (113 [48.3%] patients in the CT-P47 group and 119 [50.2%] patients in the RoActemra group).

- Grade 3 or higher TEAEs were reported for 27 (11.5%) and 31 (13.1%) patients in the CT-P47 and EU-RoActemra groups, respectively. The most frequently reported Grade 3 or higher TEAE by PT was neutropenia (7 [3.0%] and 10 [4.2%] patients, respectively); all other PTs were mostly single occurrences in either treatment group.
- Grade 4 events during Treatment Period I comprised neutropenia in one patient in both treatment groups, and coronary artery stenosis and myocardial ischaemia in one patient in the EU-RoActemra group. No Grade 5 TEAEs were reported in either treatment group during Treatment Period I.
- Apart from infectious TEAEs as discussed below, the analysis of reported AESIs identified no trends for differences.
- For both haematology and clinical chemistry parameters, individual post-baseline changes grade 3 or greater were overall infrequent and identified no concerning trends.

- *During Treatment Period II,*
  - 777 TEAEs were reported in 294 (66.2%) patients with a similar proportion of patients experiencing TEAEs among the 3 groups (149 [66.2%], 74 [67.9%] and 71 [64.5%] patients in the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups, respectively). The majority of TEAEs were grade 1 or 2 in intensity.
  - Out of all events, TEAEs in 190 (42.8%) patients were considered by the investigator to be related to the study drug, with a similar proportion among the 3 groups (95 [42.2%], 50 [45.9%] and 45 [40.9%] patients in the CT-P47 maintenance, RoActemra maintenance, and switched to CTP47 groups, respectively).
  - The most frequently reported TEAE considered by the investigator to be related to the study drug was ALT increased in all 3 groups (21 [9.3%], 12 [11.0%], and 14 [2.7%] patients in the CT-P47 maintenance, RoActemra maintenance, and switched to CTP47 groups, respectively).
  - Contrary to TP I, incidence of TEAEs classified as infection was similar across study groups during TP II: infections were reported for in total 127 (28.6%) patients, of whom 64 [28.4%], 32 [29.4%], and 31 [28.2%] patients in the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups, respectively. The other AESIs did neither show any trends for differences.
  - Number and proportion of subjects with TEAEs of grade 3 or higher was comparable across study groups: 19 (8.4%), 12 (11.0%) and 10 (9.1%) in the CT-P47 Maintenance, RoActemra Maintenance and Switched to CT-P47 groups, respectively. Grade 5 peritonitis was reported in one (0.4%) patient in the CT-P47 maintenance group.

In the single dose PK studies, AEs were reported at comparable frequencies in terms of nature and frequency.

The immunogenic potential of CT-P47 appeared comparable to EU-RoActemra:

- In the RA study 3.1
  - 6 (2.6%) and 5 (2.1%) patients in the CT-P47 and EU-RoActemra groups, respectively, were positive for ADA at Week 16 (pre-dose); all these patients were also positive for NAb.

- At Week 24 (pre-dose), 6 (2.7%) in the CT-P47 Maintenance group, 1 patient (0.9%) in the EU-RoActemra Maintenance group, and 4 patients (3.6%) in the Switched to CT-P47 group were positive for ADA; 3 (1.3%), 1 (0.9%), and 2 (1.8%) patients, respectively, were also positive for NAb.
- At Week 32 (pre-dose), 5 (2.2)% in the CT-P47 Maintenance group, 3 patients (2.8%) in the EU-RoActemra Maintenance group, and 4 patients (3.6%) in the Switched to CT-P47 group were positive for ADA; 2 (0.9%), 1 (0.9%), and 2 (1.8%) patients, respectively, were also positive for NAb.
- At Week 52 (EOS), 2 patients (0.9%) in the CT-P47 Maintenance group, 0 patients in the EU-RoActemra Maintenance group, and 3 patients (2.7%) in the Switched to CT-P47 group were positive for ADA; and none were NAb positive.
- Of note, 8 patients (3.4%) in the CT-P47 group and 11 patients (4.6%) in the EU-RoActemra group were ADA positive already at baseline, although none were positive for NAb.

- At Day 43 of the SC PK study 1.1 Part 2, 20 (13.9%) and 28 (20.0%) subjects in the CT-P47 and EU-RoActemra groups, respectively, had an ADA-positive result. Of these subjects, 17 (11.8%) and 19 (13.6%), respectively, were NAb positive.
- At Day 56 of the IV PK study 1.2, 4 (8.9%), 1 (2.3%) and 2 (4.5%) subjects in the CT-P47, EU-RoActemra groups and US-Actemra, respectively, had an ADA-positive result. Of these subjects, 2 (4.4%), 0 and 1 (2.3%), respectively, were NAb positive.

At Day 43 of PK study 1.3 comparing AI and PFS administration of CT-P47, 26 (17.0%) and 32 (20.4%) subjects in the AI and PFS groups, respectively, had an ADA-positive result. Of these subjects, 12 (7.8%) and 14 (8.9%), respectively, were NAb positive.

3.3. Uncertainties and limitations about biosimilarity

There are no remaining uncertainties and limitations that have an impact on the conclusion of biosimilarity.

3.4. Discussion on biosimilarity

Quality

The totality of the presented physicochemical and biological data supports the biosimilarity for CT-P47 and EU-RoActemra. Primary and higher order structures were shown to be broadly similar, with some differences in C-terminal lysine variants, charge variants and minor differences in glycation and purity/impurity profiles. Observed differences were appropriately discussed and shown not to be clinically meaningful, as all biological activities relevant to the MoA (sIL-6R and mIL-6R binding, inhibition of IL-6 mediated cell proliferation, competition of IL-6 and tocilizumab binding to IL-6R, dissociation of IL-6 from IL-6/sIL-6R complex by tocilizumab, and inhibitory activity on IL-6 induced downstream pathway) were similar between CT-P47 and EU-RoActemra.

Comparable binding was demonstrated to C1q and Fcγ receptors, except binding to FcγIIIa (V/F-type) and FcγIIIb receptors was lower due to overall lower galactosylation level of CT-P47. However, as Fc receptor functions do not play a role in the MoA of tocilizumab, which was appropriately demonstrated by similar lack of ADCC and CDC activity for both products, observed differences do not preclude the similarity claim. FcRn binding, known to impact on PK, was generally comparable between CT-P47 and

EU-RoActemra, and the small difference observed in IV presentations is highly unlikely to be clinically meaningful. The control strategy is adequately established to ensure consistent FcRn binding of CT-P47 batches during commercial manufacturing.

Overall, the presented comparative quality data support the biosimilarity between CT-P47 and EU-RoActemra. Observed differences are adequately discussed and justified not being clinically meaningful, and are unlikely to have an impact on PK, efficacy, or safety.

Nonclinical

From the nonclinical point of view, CT-P47 and EU-RoActemra can be considered similar in their functional activities. The cynomolgus monkey study comparing the toxicokinetic and toxicity of CT-P47 and EU-RoActemra supported the notion of lack of significant clinically relevant differences.

Clinical

Pharmacokinetics

The pivotal PK studies CT-P47 1.1 and CT-P47 1.2 in Asian healthy volunteers supported similarity of CT-P47 with EU-RoActemra after SC administration of 162 mg as PFS and after IV infusion of 8 mg/kg as the 90% for GM ratio of the three primary PK endpoints, $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}, were within the predefined conventional equivalence margins of 80.00 to 125.00%. The exploratory PK data in the efficacy/safety study CT-P47 3.1 showed no obvious differences between the CT-P47 and the EU-RoActemra. The results support the applicant's claim that there is no clinically meaningful pharmacokinetic difference between CT-P47 and the reference products (EU-RoActemra and US-Actemra), regardless of the presentation (intravenous or subcutaneous). Furthermore, Study CT-P47 1.3 demonstrated the similarity of concentration profiles between the two SC devices, CT-P47 AI and CT-P47 PFS. The results support biosimilarity of CT-P47 with EU-Roactemra.

Clinical efficacy

Efficacy results of the pivotal study CT-P47 3.1 are overall comparable across study groups in Treatment Period I between the CT-P47 and EU-Roactemra groups; and in Treatment Period II between the CT-P47, EU-Roactemra and switch groups (switch from EU-Roactemra to CT-P47), and as such support biosimilarity of CT-P47 with EU-Roactemra.

Clinical safety

Analysis of adverse event and laboratory data support the view that the safety profiles of CT-P47 and EU-RoActemra are comparable. The reported adverse event profiles seem similar in terms of nature, frequency and severity, no unexpected events or clustering was seen, and both products were generally well tolerated. The immunogenic potentials of CT-P47 and EU-RoActemra also appear to be comparable; for both products, a lower rate of ADA formation was noted with IV administration as compared to SC administration. The apparently low immunogenicity in RA patients could also be partly related to concurrent use of MTX.

The size of the safety database effectively precludes the detection of any rare adverse effects. Nevertheless, considering the extensive experience already available with the reference product and the overall evidence regarding similarity, the size can be considered sufficient in the context of a biosimilar application. To conclude, safety data from both the clinical PK studies in healthy volunteers and currently available data from the pivotal clinical study in RA patients is considered to support a determination of biosimilarity.

3.5. Extrapolation of safety and efficacy

The applicant has provided sufficient discussion regarding extrapolation of safety and efficacy across all indications applied for.

Inflammatory diseases for which RoActemra is approved are associated with enhanced IL-6 production. The molecular mode of action across all licensed indications of RoActemra is consistent and relies on tocilizumab binding to both sIL-6R and mIL-6R, preventing the interaction of IL-6 with both the IL-6R and the signal transducer gp130 complex.

EU-RoActemra is administered via IV infusions (RA, pJIA, sJIA, CRS and COVID-19) and SC injections (RA, GCA, pJIA and sJIA) in accordance with the approved posology. The same SC and IV routes of administration and the same doses as per EU-RoActemra PI were employed across CT-P47 studies and systematic evaluation of PK was carried out in conjunction with the extensive analytical program. Doses of 162 mg SC once every 1-3 weeks were approved across indications dependently on body weight and indication. The IV doses of 4-12 mg/kg are recommended dependently on the indication and body weight.

The SC and IV formulations provide similar systemic levels and the observed trough concentrations at steady state were similar across all approved indications. The applicant reviews literature showing consistent PK of tocilizumab across all licensed RoActemra indications. The applicant also refers to the information in the Actemra USPI that the MAH for Actemra/ RoActemra utilised the data from RCTs and population PK data to extrapolate the data derived from IV studies towards SC administered formulation for GCA, pJIA, sJIA indications.

While historical data demonstrates that there are some differences in the incidences of AEs and AESIs across indications, the observable differences in incidence rates are considered to be generally attributable to the differences in patient population and effects of concomitant immunomodulatory therapies. After taking into consideration these factors, the adverse event profile of RoActemra is considered to be generally similar across the approved indications.

Extrapolation to all indications of RoActemra is considered possible.

3.6. Additional considerations

N/A

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Avtozma is considered biosimilar to RoActemra. 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 Avtozma is favourable in the following indication(s):

Avtozma 20 mg/mL concentrate for solution for infusion

Avtozma, in combination with methotrexate (MTX), is indicated for:

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma 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.

Avtozma is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Avtozma is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Avtozma can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Avtozma in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older.

Avtozma 162 mg solution for injection in pre-filled syringe.

Avtozma, in combination with methotrexate (MTX), is indicated for

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma 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.

Avtozma is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Avtozma can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Avtozma in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients.

Avtozma 162 mg solution for injection in pre-filled pen.

Avtozma, in combination with methotrexate (MTX), is indicated for

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma 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.

Avtozma is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 12 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids (see Section 4.2). Avtozma can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Avtozma in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 12 years of age and older, who have responded inadequately to previous therapy with MTX (see Section 4.2). Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients.

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

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

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall provide an educational pack covering the therapeutic indications RA, sJIA, pJIA and GCA, targeting all physicians who are expected to prescribe/use Avtozma containing the following:

- Physician Information Pack
- Nurse Information Pack
- Patient Information Pack

The MAH must agree the content and format of the educational material, together with a communication plan (including means of distribution), with the national competent authority prior to distribution of the educational material.

The Physician Information pack should contain the following key elements:

- Reference to the Summary of Product Characteristics (e.g., link to EMA website)
- Dose calculation (RA, sJIA and pJIA patients), preparation of infusion and infusion rate
- Risk of serious infections
    - The product must not be given to patients with active or suspected infection
    - The product may lessen signs and symptoms of acute infection delaying the diagnosis
- Risk of Hepatotoxicity
    - Caution should be exercised when considering initiation of tocilizumab treatment in patients with elevated transaminases ALT or AST above 1.5x ULN. In patients with elevated ALT or AST above 5x ULN treatment is not recommended.
    - In RA, GCA, pJIA and sJIA, ALT/AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. The recommended dose modifications, including tocilizumab discontinuation, based on transaminases levels, in line with SmPC section 4.2.
- Risk of gastrointestinal perforations especially in patients with history of diverticulitis or intestinal ulcerations
- Details on how to report serious adverse drug reactions
- The Patient Information Packs (to be given to patients by healthcare professionals)
- Guidance on how to diagnose Macrophage Activation Syndrome in sJIA patients
- Recommendations for dose interruptions in sJIA and pJIA patients

The Nurse Information Pack should contain the following key elements:

- Prevention of medical errors and injection/infusion related reactions
    - Preparation of injection/infusion
    - Infusion rate
- Monitoring of the patient for injection/infusion related reactions
- Details on how to report serious adverse reactions

The Patient Information Pack should contain the following key elements:

- Package leaflet (with instructions for use for SC) (e.g., link to EMA website)
- Patient alert card
- to address the risk of getting infections which can become serious if not treated. In addition, some previous infections may reappear.
- to address the risk that patients using Avtozma may develop complications of diverticulitis

which can become serious if not treated.

- to address the risk that patients using Avtozma may develop serious hepatic injury. Patients would be monitored for liver function tests. Patients should inform their doctor immediately if they experience signs and symptoms of liver toxicity including tiredness, abdominal pain and jaundice.

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

Not applicable.