20 July 2023
EMA/365561/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tyenne

International non-proprietary name: tocilizumab

Procedure No. EMEA/H/C/005781/0000

Note

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

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Administrative information

Name of the medicinal product:	Tyenne
Applicant:	Fresenius Kabi Deutschland GmbH Else-Kröner Strasse 1 61352 Bad Homburg GERMANY
Active substance:	tocilizumab
International Non-proprietary Name/Common Name:	tocilizumab
Pharmaco-therapeutic group (ATC Code):	immunosuppressants, interleukin inhibitors (L04AC07)
Therapeutic indication(s):	Tyenne, 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, Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tocilizumab 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. Tyenne 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 iv formulation*) Tyenne 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. Tyenne can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX. Tyenne 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. Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tyenne 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 IV formulation*). Tyenne is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients (*only SC formulation*).
Pharmaceutical form(s):	Concentrate for solution for infusion; Solution for injection
Strength(s):	20 mg/ml and 162 mg
Route(s) of administration:	Intravenous use and Subcutaneous use
Packaging:	Vial (glass), Pre-filled syringe (glass) and pre-filled syringe (glass) in a pre-filled pen
Package size(s):	1 vial, 4 (4 x 1) vials (multipack), 1 pre-filled pen, 1 pre-filled syringe, 12 (3 x 4) pre-filled pens (multipack), 12 pre-filled syringes, 4 pre-filled pens, 4 pre-filled syringes

Table of contents

List of abbreviations

ACR	American College of Rheumatology
ACR20	20% improvement in ACR Core Set Measurement
ADA	Antidrug antibody
AE	Adverse event
AESI	Adverse event of special interest
AI	Auto-injector
ATC	Anatomical Therapeutic Chemical
AUC	Area under plasma concentration-time curve
AUC0-∞	Area under the concentration-time curve from time 0 extrapolated to infinity
AUC0-t	Area under the concentration-time curve up to the last quantifiable concentration
AUC0-72	Area under the concentration time curve from 0 to 72 hours
AUE	Area under the effect-time curve
BSSR	Blinded sample size re-estimation
CAR	Chimeric antigen receptorCPV
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Clearance
CL/F	Total apparent clearance
CMA	Critical material attribute
Cmax	Maximum observed concentration
COVID-19	Coronavirus Disease 2019
CQA	Critical quality attribute
CPP	Critical process parameter
CPV	Continuous process verification
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSR	Clinical Study Report
Ctrough	Trough concentration
CV	Coefficient of variation
DAS28-CRP	Disease Activity Score C-Reactive Protein
DAS28-ESR	Disease Activity Score 28-Erythrocyte Sedimentation Rate
DMARD	Disease-modifying antirheumatic drug
DP	Drug product
DS	Drug substance
DSP	Downstream processing
ECG	12-lead electrocardiogram
ECL	Electrochemiluminescence
Emax	Maximum observed effect
Emin	Minimum observed effect
EP-SAF	Extended treatment period safety analysis set
EULAR	European College Against Rheumatism
EU-RoActemra	EU-approved reference medicinal product RoActemra
ExCB	Extended cell bank
GCA	Giant cell arteritis
GCP	Good clinical practice
GLSM	Geometric least squares mean
GMR	Geometric mean ratio
HMW	High molecular weight
ICE	Intercurrent events
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IgG1κ	Immunoglobulin gamma 1, kappa subclass
IL-6	Interleukin-6
IL-6R	Interleukin-6 receptor
IMP	Investigational medicinal product
INN	International non-proprietary name
IPC	In-process control
IRS	Interim reference standard

IRT	Interactive response technology
ISI	Integrated summary of immunogenicity
ISR	Injection site reaction
ITT	Intent-to-treat
IV	Intravenous
JIA	Juvenile idiopathic arthritis
LLOQ	Lower limit of quantification
LS	least squares
LMW	Low molecular weight
MAA	Marketing authorisation application
mAb	Monoclonal antibody
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
mIL-6R	Membrane bound interleukin-6 receptor
MoA	Mechanism of action
MTX	Methotrexate
N/A	Not applicable
n	Number of observations
NAb	Neutralising antibody
PAR	Proven acceptable range
pCPP	Potential critical process parameter
PD	Pharmacodynamic(s)
PFS	Pre-filled syringe
PK	Pharmacokinetic(s)
PJIA	Polyarticular juvenile idiopathic arthritis
PP	Per protocol
PPQ	Process performance qualification
PTMs	Post-translational modifications
QC	Quality control
RA	Rheumatoid arthritis
rhIL-6	Recombinant human interleukin-6
RMP	Reference medicinal product
RP	Reference product
SAE	Serious adverse event
SAF	Safety analysis set
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SD	Standard deviation
sIL-6R	Soluble interleukin-6 receptor
SJIA	Systemic juvenile idiopathic arthritis
SOC	System organ class
SPR	Surface plasmon resonance
SAP	Statistical analysis plan
t1/2	Terminal elimination half-life
TEAE	Treatment emergent adverse event
Tlast	Time of last quantifiable concentration
Tmax	Time to Cmax
TNF	Tumour necrosis factor
US	United States
US-Actemra	US-licensed reference product Actemra
USP	Upstream processing
WCB	Working cell bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Fresenius Kabi Deutschland GmbH submitted on 22 July 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Tyenne, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 October 2020

The applicant applied for the following indications:

Tyenne 20 mg/mL concentrate for solution for infusion

"Tyenne, 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, Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tocilizumab 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.

Tyenne 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.

Tyenne 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. Tyenne can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Tyenne 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.

Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tyenne 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."

Tyenne 162 mg solution for injection in pre-filled syringe

"Tyenne, 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, Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tocilizumab 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.

Tyenne 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. Tyenne can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Tyenne 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.

Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

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

Tyenne 162 mg solution for injection in pre-filled pen

"Tyenne, 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, Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tocilizumab 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.

Tyenne 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). Tyenne can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Tyenne 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).

Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tyenne 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 products

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: 15-01-2009
- 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: 15-01-2009
- 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
- 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: EU/1/08/492/007, EU/1/08/492/008
- Product name, strength, pharmaceutical form:

  RoActemra, 162 mg, Solution for injection in pre-filled pen
- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 12-04-2018

- 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: 15-01-2009
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number(s): EU/1/08/492/001, EU/1/08/492/002, EU/1/08/492/005
- 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): MS200740-0001 (single-dose, SC administration); FKS456-002 (single-dose IV administration); FKS456-003 (PFS vs AI).

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
26 May 2016	EMEA/H/SA/3323/1/2016/III
27 June 2019	EMEA/H/SA/3323/1/FU/1/2019/II
24 June 2021	EMA/SA/0000060099

The applicant received scientific advice on the development of tocilizumab for the same indications as approved for the reference product RoActemra from the CHMP on 26 May 2016 (EMEA/H/SA/3323/1/2016/III). The scientific advice pertained to the following quality and clinical development aspects:

- Quality: Proposed methods to ascertain comparability
- Clinical: Design of the proposed PK/PD study, design of the proposed efficacy, safety, and immunogenicity study in RA patients, overall clinical development plan and immunogenicity assays.

The applicant received scientific advice on the development of tocilizumab for the same indications as approved for the reference product RoActemra from the CHMP on 27 June 2019 (EMEA/H/SA/3323/1/FU/1/2019/II). The scientific advice pertained to the following clinical aspects:

- Clinical: Design of the Phase III Study including proposed primary endpoint, equivalence margin, primary analysis population, primary analysis population, and proposed PK evaluations.

The applicant received scientific advice on the development of tocilizumab for the same indications as approved for the reference product RoActemra from the CHMP on 24/06/2021 (EMA/SA/0000060099). The scientific advice pertained to the following quality and clinical aspects:

- Quality: Strategy to ascertain comparability for drug substance and drug products throughout development.
- Clinical; Proposed data access plan, selection and definition of estimands, and proposed statistical analyses for study FKS456-001, approach to determining similarity at PK level.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Frantisek Drafi

The application was received by the EMA on	22 July 2022
The procedure started on	18 August 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	07 November 2022
The CHMP Co-Rapporteur's Critique was circulated to all CHMP and PRAC members on	21 November 2021

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 November 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 December 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 March 2023
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	02 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 May 2023
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	25 May 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 June 2023
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	03 July 2023
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 Tyenne on	20 July 2023

2. Scientific discussion

2.1. Problem statement

Not applicable for a biosimilar.

2.2. About the product

MSB11456 has been developed as a proposed tocilizumab biosimilar to US-licensed Actemra (US-licensed reference product, referred to as US-Actemra in the remainder of the document) and EU-approved RoActemra (EU-RoActemra) in the remainder of the document) for subcutaneous (SC) and intravenous (IV) use for approval in the European Union (EU)

The active substance, tocilizumab, is a recombinant humanised anti-human interleukin-6 (IL-6) receptor (IL-6R) monoclonal antibody (mAb) of the immunoglobulin gamma 1, kappa subclass (IgG1κ) directed against both the membrane-bound IL-6 receptor (mIL-6R) and the soluble IL-6 receptor (sIL-6R).

Tocilizumab belongs to the pharmacotherapeutic group antineoplastics and immunomodulating agents, immunosuppressants, interleukin inhibitors. The anatomical therapeutic chemical (ATC) Code is L04AC7.

The applicant is seeking approval for Tyenne for both administration routes and all indications for the reference medicinal product EU-RoActemra, namely:

1. Rheumatoid arthritis (RA) (IV and SC route)
2. Systemic juvenile idiopathic arthritis (SJIA) in patients 1 year (SC route) / 2 years (IV route) of age and older
3. Juvenile idiopathic polyarthritis (PJIA) in patients 2 years of age and older (IVC and SC route)
4. Giant cell arteritis (GCA) (SC route)
5. Chimeric antigen receptor (CAR)-T cell-induced severe or life-threatening CRS in adults and pediatric patients 2 years of age and older (IV route)
6. Coronavirus disease 2019 (COVID-19) in hospitalised adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation (IV route)

As for the reference product, the use of MSB11456 in the treatment of RA, PJIA, and SJIA is proposed for both the IV and SC routes of administration, whereas treatment of GCA is through the SC route and treatment of CRS and COVID-19 disease is through the IV route only.

2.3. Type of Application and aspects on development

The clinical development programme for MSB11456 consisted of three phase 1 studies where two included healthy individuals with the objective to evaluate PK comparability of intravenous administration of MSB11456 versus US-Actemra (FK 456-002) and for subcutaneous administration of MSB11456 versus EU-RoActemra/US-Actemra (MS200740-0001). A third study (FK456-003) included healthy participants with the aim to evaluate PK equivalence in pre-filled syringe versus auto-injector (AI) administration of MSB114556. All studies are finalised.

The demonstration of biosimilarity of MSB111456 to RoActemra is based on the totality of evidence data of analytical, nonclinical, and clinical comparative studies to demonstrate structural and functional similarity.

Data submitted within this application concerns results from study (FKS456-001), a randomised, double-blind, multiple-dose, parallel-group, two arm clinical study conducted in patients with moderately to severely active RA who have experienced an inadequate clinical response to at least one DMARD (either synthetic or biologic) and are currently receiving a stable dose of methotrexate. The overall aim is to evaluate efficacy, safety, and immunogenicity similarity of MSB11456 to EU-RoActemra. The study includes 604 patients with RA (302 in each treatment arm) that were randomised to either MSB11456 or EU-RoActemra Single use prefilled syringe (PFS) 162 mg tocilizumab/0.9 mL solution for SC injection administered every week.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented in a vial as a concentrate for solution for infusion containing 20 mg/mL of tocilizumab and as a solution for injection, in either a pre-filled syringe (PFS) or a pre-filled pen (PFP). Each vial (type I glass) contains 4 mL, 10 mL or 20 mL of concentrate (20 mg/mL). Each PFS and PFP contains 162 mg of tocilizumab in 0.9 mL.

Other ingredients are: L-arginine, L-histidine, L-lactic acid, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid and water for injections.

2.4.2. Active Substance

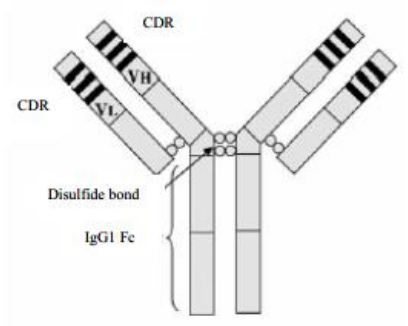
2.4.2.1. General information

The active substance (AS) tocilizumab (MSB11456) is a monoclonal recombinant humanised immunoglobulin G subclass 1 (IgG1) type antibody, composed of two covalently linked heterodimers, each of which consists of a heavy and a light polypeptide chain. One canonical N-glycosite is present at Asn299 of the heavy chain. The amino acid sequence and the properties of the antibody are acceptably presented in the dossier. The molecular weight (MW) is 148 kDa.

The proposed mechanism of action (MoA) is inhibition of IL-6-mediated signalling, through binding to membrane-bound IL-6 receptor (mIL-6R) and soluble IL-6 receptor (sIL-6R).

The information provided in this section is found acceptable.

Figure 1 Structure of Tocilizumab



CDR: Complementarity-Determining Region; Fc: Fragment crystallizable; VH: Variable region heavy chain; VL: Variable region light chain

2.4.2.2. Manufacture, characterisation and process controls

The active substance manufacturers with addresses and respective operations performed by each manufacturer, have been presented in the dossier (cell bank preparation and storage, active substance manufacturing, active substance quality control (QC) testing, active substance in-process viral and mycoplasma testing). The information is considered to be sufficient.

All relevant sites are GMP compliant. Hence, no GMP inspections are deemed necessary at this stage within the scope of this MAA evaluation procedure.

Description of manufacturing process and process controls

The monoclonal antibody (mAb) tocilizumab is manufactured at the Merck Serono facility located in Corsier-sur-Vevey, Switzerland.

Tocilizumab is expressed in Chinese hamster ovary (CHO) cells. The cell culture is harvested via continuous centrifugation, followed by filtration. Purification consists of chromatography steps, ultrafiltration steps and additional steps for removal and inactivation of potential adventitious viral contaminants. After a final filtration, the active substance is collected in sterile bags, frozen and stored, prior to shipment to the finished product (FP) manufacturing sites.

The overview of the active substance manufacturing is acceptably described.

Upstream Process (USP)

Flow charts of the cell culture and harvest process operations are provided, including the assignment of critical process parameters and associated in-process controls (IPCs) to each unit operation.

Downstream Process (DSP)

Detailed flow charts of the purification processes are provided, including the assignment of critical process parameters and associated IPCs to each unit operation. The downstream process is well described with a sufficient level of detail. Some complementary information was initially requested; this has been sufficiently provided.

Procedures for storage and shipment of the active substance are acceptably described. Process intermediate holding times are acceptably described, together with the applicable storage conditions. The storage of in-process fractions is supported by IPC microbiological data collected during large-scale manufacturing.

The proposed maximum number of reuses are acceptably described, for resins and membranes.

Reprocessing: Impact of reprocessing was evaluated.

In conclusion, the process description is found acceptable with a sufficient level of detail.

Control of materials

Cell substrate & cell banking systems

A sufficiently detailed description has been provided on the source and history of the cell substrate. The design of the plasmid and its elements have been described. Also, the transfection and selection process have been described in sufficient detail.

The primary amino acid sequence of the heavy and light chains with signal peptides are shown, and a complete annotated sequence of the plasmid has been given, indicating those regions that have been sequenced during the construction and those taken from the literature.

The preparation, establishment and characterisation of the master cell banks (MCB)-1, WCB-1.1 and ExCB-1.1.2 are presented. The cell banks are stored in the vapour phase of a liquid nitrogen containers for long-term storage and at different locations. The banks are properly identified.

The extended cell bank (ExCB) was derived from bioreactor run and further expanded. The MCB-1, WCB-1.1 and ExCB-1.1.2 were phenotypically tested and genotypically characterised. This data also supports genetic stability and is found acceptable.

A protocol for the generation of new WCBs including the preparation of related extended cell banks has been submitted and is acceptable.

Raw materials

All raw materials used are received, quarantined and released according to approved specifications and written procedures as required under current GMP. All materials comply with the European Pharmacopoeia (Ph. Eur.), or United States Pharmacopeia (USP), or with in-house specifications. Qualitative compositions are described for cell culture media, for feeds and solutions used during cell culture, and for the clarification buffer. The composition of the in-house chemically defined, medium powders and feed powder are also provided. Specifications for non-compendial materials used for cell culture media and for feeds and solutions in the production bioreactor are provided. This is found acceptable.

All media and feeds used in cell culture process are chemically defined animal component-free proprietary media. These media are free from proteins, except for the presence of insulin. Neither the insulin itself nor the raw materials used in its manufacture are derived from bovine or other animal components.

All materials used during cell culture, purification of active substance and during formulation of the finished product are of non-animal origin.

The information in the section is in general considered to be acceptable and sufficient.

Control of critical steps and intermediates

Definitions are provided for critical process parameters (CPP), proven acceptable ranges (PAR), IPC, acceptance criteria and action limits. The definitions for CPP and PAR are aligned with guidelines (ICH Q8), which is endorsed. The consequences of deviations (deviation inquiries, including an assessment on product quality impact and potential batch rejection) are acceptably described.

The CPPs and IPCs for the active substance manufacturing process are acceptably presented and summarised, after harmonisation between the process description and the CPP lists was performed, as requested.

Most of the test procedures for IPCs are the same as used for active substance release or are compendial tests. The verification of the specific procedures for the in-process tests are satisfactorily described.

Process validation and/or evaluation

Process Performance Qualification (PPQ)

The PPQ of the active substance manufacturing process was executed at the proposed commercial active substance manufacturing site, at Merck Serono S.A., Corsier-sur-Vevey (MS-Vevey), Switzerland. Demonstration of successful validation was achieved by showing that the runs were operated with process parameters within their normal operating range (NOR), and ultimately within their proven acceptable range (PAR), and by meeting the acceptance criteria on IPCs for the process intermediates, and on active substance batches. All deviations in the manufacturing process were reported and investigation(s) were conducted. The deviations are described and assessed to have no impact on product quality or process performance.

In conclusion, it is agreed that the PPQ study sufficiently demonstrates that the intended commercial manufacturing process performs as expected and produces substance meeting the active substance specification consistently. Hence, the process is considered validated.

The PPQ results are acceptably described.

Resin and Filter Lifetime Studies

The resin lifetimes were evaluated at small scale in order to establish prospectively the maximum number of cycles that can be applied in manufacturing. Adequate performance with repeated use was demonstrated by characterisation of step performance at regular intervals, including step yield and product quality. Acceptance criteria were met for all monitored attributes.

The resin and filter lifetime studies, including the conclusions, are found acceptable.

Reprocessing

Impact of reprocessing was evaluated. The validation approach is considered acceptable.

Hold Times Studies

Hold time studies were performed and the proposed hold times are considered acceptable.

Impurity clearance

An impurity clearance validation was performed. The impurities included in the evaluation were process-related impurities and product-related substances. The clearance profiles of process-related and product-related impurities demonstrated that the active substance manufacturing process is able to consistently and efficiently remove those impurities or maintain them at very low levels all along the purification process, therefore ensuring an acceptable residual quantity of process- and product-related impurities in the final active substance. The results are found acceptable.

Shipping validation

As part of the PPQ, a shipping validation has been performed with the active substance batches. The stability-indicating quality attributes of the active substance samples were tested to ensure that shipment had no adverse impact on the product quality. All samples met the acceptance criteria. The validation approach is found acceptable.

Manufacturing process development

Manufacturing process history

During development, the active substance manufacturing process has been subject to changes. Details on the changes implemented at each purification step are provided. This is found acceptable.

The history of the active substance batches and their use during development are acceptably described.

A comparability exercise was conducted to ascertain that the pre- and post-change active substance batches are comparable in terms of quality, safety and efficacy. To identify the impact of the proposed change, results were evaluated. All quality attributes studied in the comparability studies for the change of active substance show a high degree of similarity with very few and minor differences noted and are assessed as not expected to have any impact on safety or efficacy. Therefore, it can be agreed that comparability has been sufficiently demonstrated for all the attributes tested and evaluated in this comparability study.

CQA and CPP assessment

The identification of the CQAs was accomplished by using prior knowledge, experimental data and applicable published knowledge. The CQA identification is found acceptable. A final list of the CQAs has been introduced.

Process parameters were evaluated to identify the potential critical process parameters (pCPPs) based on prior knowledge derived from manufacturing and process development activities, relevant literature and scientific expertise. The approach is found acceptable.

Process characterisation studies

Process characterisation studies are presented. The expected outcome of the process characterisation studies was a list of confirmed CPPs and associated proven acceptable ranges (PARs).

Critical material attributes (CMA)

An identification of CMAs, that can have an impact on the CQAs of the active substance, was performed. Some materials were defined as critical. For these materials, risk mitigation actions were considered. The approach is considered acceptable.

Assessment of risk of nitrosamines

An assessment was performed to evaluate the risk of the presence of nitrosamine impurities in the active substance. Several potential sources were assessed. The conclusion was that the risk was negligible. The conclusion is assessed to be acceptable.

Extractables and leachables, contact materials

An evaluation of leachables and extractables from contact materials was performed on the materials with product contact during the active substance manufacturing process (excluding the active substance container, which is evaluated in Section 3.2.S.6), with an acceptable conclusion that the safety concern was negligible.

Small-scale reprocessing studies

Nanofiltration and final filtration reprocessing studies were performed at small-scale in order to evaluate the impact of repeated nanofiltrations on product quality. This was achieved by characterising the step performance and product quality over successive filtrations. All acceptance criteria were met, demonstrating that reprocessing performed at small-scale have no impact on active substance quality. The conclusion is assessed to be acceptable.

Characterisation

Elucidation of structure and other characteristics

Characterisation of MSB11456 was performed with respect to primary structure and post-translational modification (PTMs), higher order structure, purity/impurities and product related substances, general characteristics and biological characterisation. Different batches were used for characterisation, including batches manufactured by the commercial process and batches manufactured by an older version of the process. In general, state-of-the-art methods were applied and most relevant characteristics have been evaluated.

Structural and Physicochemical characterisation

Several techniques were applied to fully characterise the primary structure. Analysis of post-translational modifications was performed. Overall, the presence and levels of detected PTMs are found consistent between batches and in line with what can be expected for therapeutic monoclonal antibodies and are therefore considered acceptable.

Higher order structure was investigated. The results from all methods demonstrated acceptable higher order structure.

Biological characterisation

Biological activity characterisation for MSB11456 active substance addressed Fab binding and Fc binding. Fab binding and Fc binding were evaluated and consistent results were obtained for all batches under study. Results from a cell-based IL-6 Inhibition Bioassay are also included in the characterisation section and the choice of this cell-based assay as the sole potency assay included in the active substance and finished product specifications is found acceptably justified.

Regarding the biological characterisation, the results are further evaluated in the biosimilarity assessment exercise. In addition, analyses of Fc effector functions and intracellular signaling activities are evaluated in the biosimilarity section. This is found acceptable.

Impurities

Potential impurities and product variants of MSB11456 are categorised into the two main categories product-related substances and process-related impurities. The categorisation is found acceptable, and

the methods used for characterisation are found relevant. The results are presented and the characterisation of product-related substances is found acceptable.

The results confirm efficient removal of all process-related impurities. This is found acceptable.

2.4.2.3. Specification

Specifications

Active substance specification including methods to evaluate identity, purity, impurities, biological activity, protein content, microbiological and a few general characteristics is presented. For compendial methods, references are made to the corresponding Ph. Eur. chapters. This is found acceptable. For non-compendial method, the type of method used for analysis is stated and in-house method numbers are defined.

Justification of specification

For active substance, the acceptance criteria at release and end of shelf life are identical for all specification tests. Overall, the active substance specification criteria are aligned with the finished product specification limits at release, where applicable. This is found acceptable.

Analytical procedures and method validations

The tests for appearance, clarity, degree of coloration, pH, bioburden and bacterial endotoxins are stated to comply with Ph. Eur. This is found acceptable. Method descriptions of all non-compendial procedures are provided. For all methods, the method principle is described, the equipment, method parameters and samples to be analysed are listed. System suitability criteria are also listed, and the calculation and reporting of results are sufficiently described. Examples of typical chromatograms and electropherograms are provided. The method descriptions are found adequate and sufficient.

Comprehensive validation summaries are provided including descriptions of validation approaches, parameters, samples and obtained results. Relevant validation parameters have been evaluated. Overall, the methods were demonstrated to be adequately validated.

Batch analysis

Results from batch analysis of active substance batches are presented. Some of the batches were manufactured with the commercial process. All results complied with the proposed specification limits in place at the time of testing. The provided data from the commercial process is in support of a consistent manufacture of active substance.

Reference standards

Two different sets of reference standards have been used throughout active substance development. Initially, a one-tiered approach based on the interim reference standard (IRS) Tocilizumab 2016/01 was applied. In 2021, a two-tiered reference standard was implemented, consisting of a primary reference standard and a secondary house standard. Adequate information on the current and interim standards is provided. In conclusion, the reference standards are found sufficiently characterised.

Container Closure System

The active substance container closure is a flexible bag. The layer that contacts with the active substance is made of a copolymer, which has been demonstrated to be compliant to Ph. Eur. 3.1.7. This is found acceptable.

To demonstrate suitability of the system, the safety of product-contact materials during intended use was evaluated. An extractables and leachables assessment was carried out to provide evidence that

the container closure components do not leach harmful or undesirable amounts of substances that could pose a risk to patients. The studies, including this conclusion, are considered acceptable.

Based on the results obtained it can be concluded that the risk to patients arising from substances leaching from the proposed container closure system into active substance is negligible. This is considered acceptable.

2.4.2.4. Stability

The stability of MSB11456 active substance was tested under long-term, accelerated and stressed stability conditions. The active substance batches included in the stability programme in support of the shelf-life have been listed. The testing protocol for the PPQ batches is provided, along with the testing frequency.

For the stability studies, the container closure system is considered representative of the container routinely used for long-term storage. This is found acceptable.

For the long-term storage conditions, all results met the stability acceptance criteria and are within the limits defined for commercial specification. The results indicate that the active substance is stable under long-term intended storage conditions supporting the proposed shelf-life for the active substance.

Data from studies on accelerated and stress storage studies are acceptably presented.

2.4.3. Finished Medicinal Product (FP-IV)

2.4.3.1. Description of the product and pharmaceutical development

Finished product for intravenous administration (FP-IV) in vial, 20 mg/ml, concentrate for solution for infusion

Description and composition of the finished product

The finished product for intravenous administration (FP-IV) is a sterile, concentrated solution intended for infusion following dilution in 0.45% or 0.9% sodium chloride. It is presented at a concentration of 20 mg/mL in single dose type I glass vial closed with a bromobutyl rubber stopper and sealed with an aluminum crimp seal closure.

The components of the finished product (FP-IV) are tocilizumab, L-arginine, L-histidine, L-lactic acid, sodium chloride, polysorbate 80, hydrochloric acid (E507) and/or sodium hydroxide (E524), water for injections.

The FP-IV is available in three presentations:

-80 mg/4 mL in 6R vials

-200 mg/10 mL in 20R vials

-400 mg/20 mL in 20R vial

Each presentation includes an overfill to permit withdrawal of the required volume of not less than 4.0 mL, 10.0 mL or 20.0 mL, as applicable.

The overfills in the three presentations has been sufficiently justified.

The three presentations share the same composition and differ only in the size of the vial and the fill volume applied.

The vial, stopper and seal components are compliant with appropriate Ph. Eur. monographs for primary containers and closures and are further addressed in section P.7.

The section on description and composition of the finished product is found acceptable.

Pharmaceutical development

Formulation development

The formulation of the biosimilar candidate finished product (vial) is not identical to the EU-authorised reference medicinal product (RMP) RoActemra and the US-authorised reference product (RP) Actemra. Considering the results of the formulation development studies, a suitable and unique combination of excipients was identified.

Overages and Physicochemical and biological properties

There are no formula overages applied to the formulation of finished product-IV. The information given on physicochemical and biological properties is found sufficient.

The information provided in the dossier is found acceptable.

Manufacturing process development

The section on manufacturing process development for the finished product-IV has been sufficiently described and justifies the commercial manufacturing process.

The manufacturing process for the FP-IV consists of thawing, pooling, dilution of active substance followed by filtrations, aseptic filling, stoppering and capping. The manufacturing process development activities consisted of the definition of a Quality Target Product Profile (QTPP), identification of CQAs and characterisation of CPPs as well as the corresponding PARs. These activities provided the basis for the development of the process control strategy.

The commercial manufacturing process has been characterised through process characterisation studies of each process step and details for these studies are provided in the dossier.

The process characterisation studies demonstrate that the finished product-IV manufacturing process is robust and can deliver the required product quality and process consistency when the manufacturing process is conducted within the prescribed operating ranges.

Control strategy

The development of the control strategy for the finished product has been sufficiently described. The CPPs and IPCs for the commercial manufacturing process as well as the specifications are provided in the dossier.

Nitrosamine risk assessment and elemental impurities

A risk assessment of N-nitrosamine contamination in the finished product-IV has been performed and report has been provided. It is agreed that the risk of formation and entry of N-nitrosamine impurities is negligible in the finished product-IV.

A risk assessment of elemental impurities in the finished product-IV has been performed and results are provided. It is agreed that the residual quantity of elemental impurities is very low, and all meet the requirements specified in ICH Q3D.

Comparability

During the development, some changes have been introduced for the manufacturing process of finished product -vial. Comparability testing has been performed in accordance with ICH Q5E, based on

a combination of analytical physicochemical testing and biological assays. A comparison of quality data on pre- and post-change finished product -vial has been performed including routine batch analysis, process comparisons, extended characterisation testing and stability data. The comparability results to support the manufacturing process changes implemented are provided.

All quality attributes studied in the comparability studies show a high degree of similarity with very few and minor differences noted and are assessed as not expected to have any impact on safety or efficacy. Therefore, it can be agreed that comparability has been sufficiently demonstrated for all the attributes tested and all the finished product -vial presentations included and evaluated in this comparability study.

Batch history and specifications development

A batch history for finished product -vial has been provided.

Furthermore, it can also be noted that the history of the release specification for finished product -vial used during development and proposed for commercial manufacturing has been provided.

The information provided on manufacturing process development for finished product-IV is found sufficient and acceptable.

Container closure system

The development of the container closure system is sufficiently presented. The finished product is presented at a concentration of 20 mg/mL in single dose type I glass vial closed with a bromobutyl rubber stopper and sealed with an aluminum crimp seal closure. The finished product-IV is available in three presentations: 80 mg/4 mL in 6R vials, 200 mg/10 mL in 20R vials and 400 mg/20 mL in 20R vial. The three presentations share the same composition and differ only in the size of the vial and the fill volume applied. The vial, stopper and seal components are compliant with appropriate Ph. Eur. monographs for primary containers and closures and are further addressed in the dossier.

Microbiological attributes

The information given on microbiological attributes is found sufficient.

Compatibility

Compatibility of the finished product -vial with the infusion medium (0.9% and 0.45% sodium chloride) has been studied and satisfactorily demonstrated during development and in-use stability studies. In-use stability has been studied to simulate in-use conditions and verify the chemical and physical stability of the finished product-IV as well as to confirm the compatibility upon in-use administration with the ancillaries.

Furthermore, the applicant has provided a justification for the statement in section 6.3 in the SmPC that "After dilution in sodium chloride 9 mg/mL (0.9%) or 4.5 mg/mL (0.45%) solution, the prepared solution for infusion is stable up to 30 °C for 24 hours". This is found acceptable.

2.4.3.2. Manufacture of the product and process controls

Manufacturers

The manufacturing and testing sites for MSB11456 finished product-IV are GMP compliant. The information provided on manufacturers and batch formula is considered acceptable.

Description of manufacturing process and process controls and controls of critical steps and intermediates

The manufacturing process for the FP-IV consists of thawing, pooling, dilution of active substance followed by filtrations, aseptic filling, stoppering and capping.

The description of manufacturing process and process controls and control of critical steps and intermediates of the FP-IV is at large sufficiently described.

Acceptable ranges are provided for process parameters and in-process controls and brief process flow diagrams are provided for the manufacturing process of the FP-IV.

Hold times

Process steps durations and hold times in the FP-IV manufacturing process together with their respective hold conditions and periods have been provided. The parameters mentioned have been confirmed in the validation study submitted.

The information provided in the dossier is found sufficiently detailed.

Process validation and/or evaluation

PPQ-batches of the FP-IV were manufactured at the commercial site. Batch data are provided for all FP-IV validation batches. FP-IV validation batches complied with the established validation acceptance criteria for all process parameters and in-process controls as well as with the proposed FP-IV specifications. The validation was run at set points while the ranges of process parameters (i.e. PARs) were challenged during the manufacturing process development. Acceptable validation data are also provided with respect to maximum cumulative process and hold times.

Furthermore, the FP-IV manufacturing process will be continuously monitored in the future in a continued process verification life cycle management programme.

Comparability

During the development, some changes have been introduced for the manufacturing process of FP-vial. Acceptable comparability data in support of the changes of manufacturing sites and vial presentations for the FP-IV have been provided.

Transport validation

Shipping validation studies for the FP-IV have been performed to demonstrate that the transport at 2-8°C does not adversely impact the quality of the finished or its packaging.

The provided transport validation data are found acceptable and confirm that the quality attributes are maintained when the FP-IV is transported within 2-8°C.

Validation of the aseptic filling process

Media fills were used to validate the aseptic filling process. The media fill validation demonstrated that the aseptic conditions are maintained during the filling process.

Filter validation

As requested, a filter validation package has been provided. The provided results justify the use of these filters in commercial manufacturing of the FP-vial in-line with the requirements in the guideline EMA/CHMP/CVMP/QWP/850374/2015.

This is found acceptable.

In conclusion, the process validation data presented demonstrate that the process is robust and performs as intended, giving a finished product which meets the quality requirements when run within the defined operating ranges.

2.4.3.3. Product specification

Product specification

The specification for MSB11456 FP-IV in vial include methods to evaluate identity, purity, impurities, biological activity, protein content, microbiological and some general characteristics.

Finished product specification and justification of specifications

A large and comprehensive set of relevant tests is included in the specifications document for the FP-IV covering limits for both release and end-of-shelf-life (EOSL) of the various attributes. Separate limits are proposed at release and EOSL for all purity/impurities and product related substances.

The proposed acceptance criteria are found acceptable and clinically qualified.

In addition, the proposed acceptance criteria for the general tests, identification tests and microbiological tests are found acceptable as well.

Analytical procedures

Many tests used for release and stability testing of FP-IV are also used for release and stability testing of active substance. These methods and validation results are presented, discussed and assessed and cover both active substance and FP-IV. The analytical procedures were validated in accordance with ICH Q2 and the compendial methods have been verified according to the appropriate compendia chapters and been determined to be suitable for use.

The method description and validation summary of a DP specific method are found in the dossier. The provided information is found sufficient, and the method deemed acceptably validated.

Batch analyses

Batch analysis data has been provided for FP-IV batches used for development, clinical studies, stability, process validation (PPQ-batches) as well as used in the biosimilarity exercise. The batch analysis data complies with the limits in the proposed FP-vial release specification in place at the time of testing and confirm process and product batch-to-batch consistency. In conclusion, the batch data provided demonstrate a reproducible manufacturing of FP-vial.

Impurities of the finished product

Potential process and product-related impurities are sufficiently addressed. It has been shown that no new impurities/product-related substances are generated during manufacture of the FP-IV. Leachables and extractables are discussed.

Furthermore, a risk assessment of N-nitrosamine contamination in the FP-IV has been performed and a report has been provided. It is agreed that the risk of formation and entry of N-nitrosamine impurities is negligible in the FP-IV. A risk assessment of elemental impurities in the FP-IV has been performed and results are provided. It is agreed that the residual quantity of elemental impurities is very low, and all meet the requirements specified in ICH Q3D.

Container closure system

The development of the container closure system has been sufficiently described. It is presented at a concentration of 20 mg/mL in single dose type I glass vial closed with a bromobutyl rubber stopper and sealed with an aluminum crimp seal closure and secondary packaged in a cartoon box. The FP-IV

is available in three presentations: 80 mg/4 mL in 6R vials, 200 mg/10 mL in 20R vials and 400 mg/20 mL in 20R vial. The three presentations share the same composition and differ only in the size of the vial and the fill volume applied.

The primary packaging material has been acceptably described and include schematic drawings, dimensions and the quality standards. The vials and stoppers are in compliance with the Ph. Eur. monographs for primary containers (Ph. Eur. 3.2.1) and closures (Ph. Eur. 3.2.9). Furthermore, information on the supplier of the primary packaging material has been provided.

2.4.3.4. Stability of the product

The proposed shelf-life for the FP-vial is 36 months when stored at the recommended storage condition of 2°C to 8°C.

The applicant has provided results up to 36 months at long-term storage condition of 2°C to 8°C for batches of FP-vial, 400 mg/20 mL. In addition, stability data has also been provided at accelerated and stressed conditions as well as for in-use stability studies, temperature cycling and photostability testing.

It can be noted that comparability has been successfully demonstrated between the FP-vial manufactured at different sites as well as between all three FP-IV (vial) presentations (400 mg/20 mL, 200 mg/10 mL and 80 mg/4 mL).

The stability studies are performed in accordance with ICH Q5C and the container closure system used in the stability studies is identical with the proposed commercial container closure system as described in the dossier for the FP-vial.

All stability results available at long-term storage conditions up to 36 months complies with the proposed end-of-shelf-life/stability specifications.

At accelerated and stressed conditions all batches revealed more pronounced degradation patterns over time.

Compatibility of the FP-vial with the infusion medium (0.9% and 0.45% sodium chloride) has been studied and satisfactorily demonstrated during development and in-use stability studies. In-use stability has been studied to simulate in-use conditions and verify the chemical and physical stability of the FP-IV as well as to confirm the compatibility upon in-use administration with the ancillaries.

Furthermore, as requested, the applicant has provided a justification for the in-use stability statement in section 6.3 in the SmPC that "After dilution in sodium chloride 9 mg/mL (0.9%) or 4.5 mg/mL (0.45%) solution, the prepared solution for infusion is stable up to 30 °C for 24 hours" and section 3.2.P.8 has been updated. 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 2–8 °C and up to 8 hours at 30 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Photostability testing has been performed according to ICH Q1B and this study showed that the FP-vial should be kept in the outer cartoon in order to protect from light induced degradation, in line with the wording in section 6.4 in the SmPC.

A temperature cycling study has been performed and all results met the proposed acceptance criteria during the study.

Post-approval stability protocol and stability commitment

The applicant commits to complete all the ongoing stability studies according to the submitted protocol. The batches will be tested according to the protocol provided. The annual post-approval stability protocol is found acceptable.

Proposed shelf life and storage conditions

The proposed shelf-life for FP-IV at the recommended storage conditions of at 2-8°C is 36 months when stored in the commercial container protected from light.

In addition, after dilution with saline solution (0.9% or 0.45% sodium chloride solution) the FP-IV solutions may be stored up to 24 hours at 2-8°C or up to 8 hours at controlled room conditions up to 30°C protected from light.

The proposed shelf-life is found acceptable.

2.4.4. Finished Medicinal Product (FP-SC)

2.4.4.1. Description of the product and pharmaceutical development

Finished product for subcutaneous administration (FP-SC), 180 mg/ml, solution for injection in pre-filled syringe and/or in pre-filled pen

Description and composition of the finished product

The finished product for subcutaneous administration (FP-SC) is presented as a sterile, ready to use, single dose solution for injection at a nominal concentration of 180 mg/mL in a 1 mL type I glass syringe combined with a 27G ½ inch (12.7 mm) staked stainless steel needle protected by a rigid needle shield, closed with a bromobutyl rubber (plunger stopper).

The solution (FP-SC) contains L-arginine, L-histidine, L-lactic acid, Sodium chloride, Polysorbate 80 Hydrochloric acid (E507) and/or sodium hydroxide (E524) (for pH adjustment), Water for injections.

The overfill in the PFS has been sufficiently justified.

The pre-fillable syringe and plunger stopper are compliant with appropriate Ph. Eur. monographs for primary containers and closures and are further addressed in section P.7.

The section on description and composition of the finished product is found acceptable.

Pharmaceutical development

Formulation development

The formulation of the biosimilar candidate FP-SC is not identical to the EU-authorised reference medicinal product (RMP) RoActemra and the US-authorised reference product (RP) Actemra. Considering the results of the formulation development studies, a suitable and unique combination of excipients was identified.

Overages and Physicochemical and biological properties

There are no formula overages applied to the formulation of FP-SC. The information given on physicochemical and biological properties is found sufficient.

The information provided in the dossier is found acceptable.

Manufacturing process development

The section on manufacturing process development for the FP-SC has been sufficiently described and justifies the commercial manufacturing process.

The manufacturing process for the FP-SC consists of thawing, pooling, dilution of active substance followed by compounding of final finished product in concentrated excipient solution, filtrations, aseptic filling in the syringes and insertion of the plunger stoppers. The filled syringes are then assembled with an needle safety device or auto-injector device.

The manufacturing process development activities consisted of the definition of a QTPP, identification of CQAs, establishing the linkage between CQAs and potential CPPs and characterisation of CPPs as well as the corresponding PARs. These activities provide the basis for the development of the process control strategy.

The commercial manufacturing process has been characterised through process characterisation studies of each process step and details for these studies are provided in the dossier.

Furthermore, it can also be noted that the manufacturing process for both FP-SC and FP-IV is similar except for the dilution to the required tocilizumab concentration and filling. Due to these similarities a number of process characterisation studies are applicable to both FP-SC and FP-IV.

The process characterisation studies demonstrate that the FP-SC manufacturing process is robust and can deliver the required product quality and process consistency when the manufacturing process is conducted within the prescribed operating ranges.

Control strategy

The development of the control strategy for the finished product has been sufficiently described. The CPPs and IPCs for the commercial manufacturing process as well as the specifications are provided in the dossier.

Nitrosamine risk assessment and elemental impurities

A risk assessment of N-nitrosamine contamination in the FP-SC has been performed and the report has been provided in module 1. It is agreed that the risk of formation and entry of N-nitrosamine impurities is negligible in the FP-SC.

A risk assessment of elemental impurities in the FP-IV has been performed and results are provided. It is agreed that the residual quantity of elemental impurities is very low, and all meet the requirements specified in ICH Q3D.

Comparability

During the development, some changes have been introduced for the manufacturing process of FP-SC. Comparability testing has been performed in accordance with ICH Q5E, based on a combination of analytical physicochemical testing and biological assays. A comparison of quality data on pre- and post-change FP-vial has been performed including routine batch analysis, process comparisons, extended characterisation testing and stability data. The comparability results to support the manufacturing process changes implemented are provided. All quality attributes studied in the comparability studies show a high degree of similarity with very few and minor differences noted and are assessed as not expected to have any impact on safety or efficacy. Therefore, it can be agreed that comparability has been sufficiently demonstrated for all the attributes tested and evaluated in this comparability study.

Batch history and specifications development

A batch history for FP-SC has been provided.

Furthermore, it can also be noted that the history of the release specification for FP-SC used during development and proposed for commercial manufacturing has been provided.

The information provided on manufacturing process development for the FP-SC is found sufficient and acceptable.

Container closure system

The development of the container closure system is sufficiently presented. The finished product for subcutaneous administration is presented as a sterile, ready to use, single dose solution for injection at a nominal concentration of 180 mg/mL in a 1 mL type I glass syringe combined with a 27G ½ inch (12.7 mm) staked stainless steel needle protected by a rigid needle shield, closed with a bromobutyl rubber plunger stopper.

The pre-fillable syringe and plunger stopper are compliant with appropriate Ph. Eur. Monographs for primary containers and closures and are further addressed in the dossier.

The PFS is further permanently assembled with either a needle safety device or an auto-injector device.

The suitability of the container closure system to protect the content from microbial contamination during storage, transportation and use of FP-SC was demonstrated during long-term stability and shipping validation studies, results are provided in the dossier.

Furthermore, the suitability of the container closure system was confirmed by the results of the extractables and leachables testing.

Microbiological attributes

The information given on microbiological attributes is found sufficient.

Compatibility

Compatibility of FP-SC with the container closure system has been demonstrated by development studies and stability data. The FP-SC is not in direct contact with the anti-needle stick device and AI device.

No reconstitution diluents are being used to administer FP-SC.

The information provided with respect to container closure system, microbiological attributes and compatibility is found sufficient and acceptable.

2.4.4.2. Manufacture of the product and process controls

Manufacturers

All the manufacturing and testing sites for MSB11456 FP-SC are GMP compliant. The information provided on manufacturers and batch formula is considered acceptable.

Description of manufacturing process and process controls and controls of critical steps and intermediates

The manufacturing process for the FP-SC consists of thawing, pooling, dilution of active substance followed by compounding of final finished product in concentrated excipient solution, filtrations, aseptic filling in the syringes and insertion of the plunger stoppers. The filled syringes are then assembled with a needle safety device or auto-injector device.

The description of manufacturing process and process controls and control of critical steps and intermediates of the FP-SC is found sufficiently described.

Acceptable ranges are provided for process parameters and in-process controls and brief process flow diagrams are provided for the manufacturing process of the FP-SC.

The in-process controls and hold times for the PFS assembly into the needle safety device and in the auto-injector device) have also been defined and they also include acceptable acceptance criteria.

Hold times

Process steps durations and hold times in the FP-SC manufacturing process together with their respective hold conditions and periods have been provided. It could also be noted that a hold time has been defined for the PFS assembly into the needle safety device and in the auto-injector device. The parameters mentioned have been confirmed in the validation study.

The information provided in the dossier is found sufficiently detailed.

In addition, IPCs are performed during PFS assembly into the autoinjector. It is found acceptable that this testing is performed in-process at the level of FP-SC.

Process validation and/or evaluation

PPQ-batches of the FP-SC were manufactured at the commercial site. Batch data are provided for all FP-SC validation batches.

FP-SC validation batches were manufactured from active substance-batches manufactured at the commercial active substance-manufacturing site and they all complied with the established validation acceptance criteria for all process parameters and in-process controls as well as with the proposed FP-SC specifications. The validation was run at set points while the ranges of process parameters (i.e. PARs) were challenged during the manufacturing process development. Acceptable validation data are also provided with respect to maximum cumulative process and hold times.

Furthermore, the FP-SC manufacturing process will be continuously monitored in the future in a continued process verification life cycle management programme.

Process validation for assembly of a needle safety device and AI device

Validation results have been provided from validation studies of the assembly of the needle safety device and AI device that successfully demonstrates that the assembly process does not compromise the finished product integrity and is capable to deliver combination products fulfilling all the quality, safety and functional requirements.

Based on the available validation results, the assembly process of the FP-SC into the needle safety device as well as into the AI device is considered successfully validated.

Comparability

During the development, some changes have been introduced for the manufacturing process of FP-SC. Acceptable comparability data in support of the changes of manufacturing sites and change in hold tank size has been provided.

Transport validation

Shipping validation studies for the FP-SC have been performed to demonstrate that the transport at 2-8 °C does not adversely impact the quality of the finished product or its packaging.

The provided transport validation data are found acceptable and confirm that the quality attributes are maintained when the FP-SC is transported within 2-8°C.

Validation of the aseptic filling process

Media fills were used to validate the aseptic filling process. The media fill validation demonstrate that the aseptic conditions are maintained during the filling process.

Filter validation

As requested, a filter validation package has been provided. The provided results justify the use of these filters in commercial manufacturing of the FP-vial in-line with the requirements in the guideline EMA/CHMP/CVMP/QWP/850374/2015.

This is found acceptable.

In conclusion, the process validation data presented in section P.3.5 demonstrate that the process is robust and performs as intended, giving a FP-SC which meets the quality requirements when run within the defined operating ranges.

2.4.4.3. Product specification

Product specification

The specification for MSB11456 FP-SC includes methods to evaluate identity, purity, impurities, biological activity, protein content, microbiological and some general characteristics.

Finished product specification and justification of specifications

A large and comprehensive set of relevant tests is included in the specifications document for the FP-SC covering limits for both release and end-of-shelf-life (EOSL) of the various attributes. Separate limits are proposed at release and EOSL for all purity/impurities and product related substances.

The proposed acceptance criteria are found acceptable and clinically qualified.

In addition, the proposed acceptance criteria for the general tests, identification tests and microbiological tests are found acceptable as well.

In addition, it is acknowledged and found acceptable that testing of other relevant parameters of device functionality is performed in-process at the level of assembly of both the pre-filled syringe and the pre-filled pen/autoinjector.

Moreover, the applicant has also tested functional device parameters during long term stability studies. Stability data has been provided on aged samples, up to 24 months at normal long-term storage conditions. All results complied with the specifications demonstrating that these parameters for device functionality remain compliant with the acceptance criteria during long-term storage and the shelf life of the assembled finished product.

Analytical procedures

Many tests used for release and stability testing of FP-SC are also used for release and stability testing of active substance. These methods and validation results are presented, discussed and assessed and cover both active substance and FP-SC. The analytical procedures were validated in accordance with ICH Q2 and the compendial methods have been verified according to the appropriate compendia chapters and been determined to be suitable for use.

The method description and validation summary of the DP specific method are found in the dossier. The provided information is found sufficient, and the method deemed acceptably validated.

Batch analyses

Batch analysis data has been provided for FP-SC batches used for development, clinical studies, stability, process validation (PPQ-batches) as well as used in the biosimilarity exercise. The batch analysis data complies with the limits in the proposed FP-SC release specification in place at the time of testing and confirm process and product batch-to-batch consistency. In conclusion, the batch data provided demonstrate a reproducible manufacturing of FP-SC.

Impurities of the finished product

Potential process and product-related impurities are sufficiently addressed. It has been shown that no new impurities/product-related substances are generated during manufacture of the FP-SC. Leachables and extractables are discussed.

Furthermore, a risk assessment of N-nitrosamine contamination in the FP-SC has been performed and a report has been provided. It is agreed that the risk of formation and entry of N-nitrosamine impurities is negligible in the FP-SC. A risk assessment of elemental impurities in the FP-SC has been performed and results are provided. It is agreed that the residual quantity of elemental impurities is very low, and all meet the requirements specified in ICH Q3D.

This is found acceptable.

Container closure system

The development of the container closure system has been sufficiently described. The finished product for subcutaneous administration is presented as a sterile, ready to use, single dose solution for injection at a nominal concentration of 180 mg/mL in a 1 mL type I glass syringe combined with a 27G ½ inch (12.7 mm) staked stainless steel needle protected by a rigid needle shield, closed with a bromobutyl rubber (plunger stopper).

Acceptable dimensional drawings and specifications are provided for the glass syringe barrel with staked needle and rigid needle shield and the rubber plunger stopper. Compliance to the requirements in the Ph. Eur. monographs 3.2.1 (Glass containers for Pharmaceutical use) and 3.2.9 (Rubber closures) has been demonstrated. Furthermore, as requested, information on the supplier of primary packaging material has been provided and included in the dossier.

The sterilisation of the glass syringe barrel and the rubber plunger stopper are performed at standard conditions. The specifications for both the glass syringe barrel and the rubber plunger stopper include testing for sterility (Ph. Eur. 2.6.19) and bacterial endotoxins (Ph. Eur. 2.6.14). This is found acceptable.

The PFS is further permanently assembled with either a needle safety device or an auto-injector device. The PFS and the auto-injector forms two combination products and integral medicinal devices. Further details on these two combination products and integral devices as well as their corresponding Notified Body Opinions (NBOp) have been provided.

Both the PFS device (needle safety device) and the autoinjector device are prefilled, single-use, injection devices intended exclusively for use in combination with MSB11456 and delivers finished product subcutaneously in a fixed-dose format.

The suitability of the container closure system to protect the content from microbial contamination during storage, transportation and use of FP-SC was demonstrated during long-term stability and shipping validation studies, and results are provided.

Validation results have been provided from validation studies of the assembly of the needle safety device and AI device that successfully demonstrates that the assembly process does not compromise

the finished product integrity and is capable to deliver combination products fulfilling all the quality, safety and functional requirements. Furthermore, the suitability of the container closure system was confirmed by the results of the extractables and leachables testing.

It has been concluded in the NBOp reports of both the PFS and the autoinjector that the design validations and usability studies as well as design verifications have been well planned, executed and successfully demonstrated as acceptable and all relevant ISO, IEC and ASTM standards and requirements met.

In conclusion, it has been demonstrated in the NBOp reports that the PFS (needle safety device) and the autoinjector meet the relevant requirements of Annex I of regulation (EU) 2017/745. Furthermore, it has also been demonstrated that the intended user population can safely and effectively operate both the PFS and the autoinjector to deliver a complete dose, using the Instructions for use, per its intended uses and use environment.

As requested, product samples of the PFS (needle safety device) and the autoinjector has been provided to assess the suitability for use. No issues were identified with respect to the assembled FP-SC samples.

2.4.4.4. Stability of the product

The proposed shelf-life for the FP-SC is 36 months when stored at the recommended storage condition of 2°C to 8°C.

The applicant has provided stability results for the FP-SC up to 48 months at long-term storage condition of 2°C to 8°C for a clinical batch. The presentations studied include both naked PFS and PFS assembled with a needle safety device or in an auto-injector device.

In addition, stability data has also been provided at accelerated and stressed conditions as well as for in-use stability studies, temperature cycling, storage at room temperature and photostability testing.

It can be noted that comparability has been successfully demonstrated between the FP-SC manufactured at different sites as well as for some other changes. The stability studies are performed in accordance with ICH Q5C and the container closure system used in the stability studies is identical with the proposed commercial container closure system for the FP-SC.

All stability results available at long-term storage conditions up to 48 months complies with the proposed end-of-shelf-life/stability specifications.

At accelerated and stressed conditions all batches revealed more pronounced degradation patterns over time.

Photostability testing has been performed according to ICH Q1B and this study showed that the FP-SC should be kept in the outer cartoon in order to protect from light induced degradation, in line with the wording in section 6.4 in the SmPC.

A room temperature study has been performed in order to support temporary storage of the FP-SC out of the refrigerator.

A temperature cycling study has been performed. All results met the proposed acceptance criteria during the study.

Post-approval stability protocol and stability commitment

The applicant commits to complete all the ongoing stability studies according to the submitted protocol in section P.8.1. The batches will be tested according to the protocol provided. The annual post-approval stability protocol is found acceptable.

Proposed shelf life and storage conditions

The proposed shelf-life for FP-SC at the recommended storage conditions of at 2-8°C is 36 months when stored in the commercial container protected from light.

In addition, the FP-SC may be stored at temperatures up to 25°C for a single period of up to 14 days. The pre-filled syringe must be protected from light, and discarded if not used within the 14 day period.

The proposed shelf-life is found acceptable.

2.4.4.5. Biosimilarity

Overall approach

MSB11456 (tocilizumab) has been developed as a proposed biosimilar to the reference medicinal product (RMP) EU-approved RoActemra and the reference product (RP) US-approved Actemra. The RMP for the MAA is EU-approved RoActemra, but bridging to US-approved Actemra is required since the RP has been used in some clinical trials.

Lots included in the biosimilarity assessment

The applicant states that MSB11456 and RoActemra are identical with respect to pharmaceutical form, concentration and route of administration and differ only in formulation. The differences in formulations are sufficiently described. The analytical biosimilarity assessment involves MSB11456 finished product, RoActemra and Actemra for both subcutaneous (SC) and intravenous (IV) administration. A table is provided, showing the number of batches included for each analytical procedure. In conclusion, the number of batches of both MSB11456 and the RMP are considered sufficient.

The age of the batches at time tested is also clearly shown. The applicant confirms that the MSB11456 batches were relatively young at the time of testing in comparison to RP/RMP batches. Therefore, an evaluation of attributes that could change on storage is included in the biosimilarity section, and reference is given to stability section 3.2.P.8. A few of the attributes were found to change over time. These attributes are included with the comparative analytical data in the relevant subsections of Section 3.2.R.1.3. Overall, the presentation of age of batches and the evaluation of impact on attributes are found acceptable. The impact on specific attributes will be assessed in conjunction with the corresponding subsections.

Analytical similarity acceptance criteria and statistical approach

Criticality ranking was performed for physicochemical and biological attributes and a criticality score was calculated for each attribute based on severity of clinical impact and the likelihood/uncertainty of clinical impact. The approach is found acceptable.

For statistical analysis, data from attributes of moderate to very high criticality were evaluated using the quality range approach, mean ±X SD. Justifications for setting X are provided for each attribute. To allow for comparison of attributes of low and very low criticality scores and attributes for which statistical analysis is not feasible, tables of data, raw data and graphical data are presented side-by-side for MSB11456, RMP and RP. Depending on the attribute, similarity is evaluated by visual comparison of the raw data such as spectra or descriptive statistics (mean and minimum to maximum ranges). It should be note that also for attributes where quality ranges are calculated, tables of data and side-by-side comparisons are presented.

Overall, the statistical approach is found acceptable. The strategy to provide graphical and tabular presentations of individual analytical results enables an assessment independent of the defined quality ranges for each attribute. From the graphical presentations, it was also concluded that the quality ranges were acceptably defined.

In conclusion, the overall approach to assess analytical similarity is found acceptable.

Table 1 Conclusions of comparative analytical studies

Attribute		Method	Results of Similarity Assessment for SC Presentations	Results of Similarity Assessment for IV Presentations
Primary Structure				
Amino acid sequence		Peptide mapping	Identical	Identical
Mass of LC and HC		Whole molecule analysis	Similar	Similar
Post-translational Modifications				
Deamidation		Peptide mapping	Similar	Similar
Oxidation			Similar	Similar
Glycation			Higher in MSB11456	Higher in MSB11456
N-glycosite occupancy			Similar	Similar
N-terminal variants			Similar or lower in MSB11456	Lower in MSB11456
C-terminal variants			Similar or lower in MSB11456	Similar or lower in MSB11456
N-terminal Sequence		Edman chemistry	Identical	Identical
Higher Order Structure				
Secondary structure		FTIR	Similar	Similar
Secondary & tertiary Structure		Circular dichroism-Near and Far UV	Similar	Similar
Thermal Stability & HOS		Nano-DSC	Highly similar	Highly similar
Tertiary structure		Fluorescence spectroscopy	Similar	Similar
Free thiol		Ellman's test	Similar	Similar
Disulphide linkage		Peptide mapping	Similar	Similar
Purity and Impurities				
Monomer & HMW species/ aggregates		SE-HPLC	Highly similar	Highly similar
		Analytical ultra-centrifugation	Similar	Similar
		SE-HPLC-MALLS	Similar	Similar
Purity & LMW species (non-assembled forms/ fragment)		CE-SDS	Highly similar	Highly similar
Subvisible particles		Low volume light obscuration	Similar or lower in MSB11456	Similar or lower in MSB11456
		MFI	Similar or lower in MSB11456	Similar or lower in MSB11456
Charge Variants				
Charge-based profile	Acidic	IEX-HPLC	Similar or higher in MSB11456	Similar or lower in MSB11456
	Basic		Similar or lower in MSB11456	Similar or higher in MSB11456
	Main		Similar or higher in MSB11456	Similar or lower in MSB11456
	Acidic	icIEF	Similar	Similar or lower in MSB11456
	Basic		Similar or lower in MSB11456	Similar
	Main		Similar	Similar or higher in MSB11456
Oxidised Species		RP-UPLC	Highly similar	Highly similar
Glycosylation				
Sialic Acids		HPAEC-PAD	Similar	Similar
Glycans		2-AB glycan mapping	Similar or higher in MSB11456	Similar or higher in MSB11456
Protein Content				
Protein concentration		Optical density	Highly similar	Highly similar
Extractable volume		Gravimetric volume determination	Highly similar	Similar or higher in MSB11456

Fab Binding and Potency			
IL-6 neutralization	IL-6 inhibition by *in vitro* bioassay	Highly similar	Highly similar
sIL-6R binding	SPR	Highly similar	Highly similar
mIL-6R binding	Flow cytometry	Highly similar	Highly similar
Fc binding			
FcRn binding	SPR	Highly similar	Highly similar
FcγR binding		Similar	Similar
C1q binding	ELISA	Similar	Similar
***In vitro* Pharmacology for Extrapolation of Indications**			
In vitro PD signalling	IL-6 induced signaling by Flow cytometry	Similar	Similar
	sIL-6R driven signaling by luminescence	Similar	Similar
Comparative *in vitro* Pharmacodynamic Studies			
ADCC	ADCC-induced cell death by luminescence	Similar lack of ADCC	-
CDC	CDC-induced cell viability reduction by luminescence	Similar lack of CDC	-
Apoptosis	Apoptosis by luminescence	Similar lack of apoptosis	Similar lack of apoptosis

Primary structure and Post-translational modifications

The primary sequence of MSB11456 and the RMP and RP was evaluated by peptide mapping. The sequence coverage was determined to be 100% for all three products.

The masses of the intact light chain and the deglycosylated heavy chain were demonstrated to comply with the theoretical molecular masses, and thus to be similar between MSB11456 and the RMP. The light chain was detected predominantly at around 23500 Da. The assignment of peaks is found accurate.

Furthermore, no results were provided for the intact molecule and also not for the glycosylated heavy chain. This is considered a limitation.

Post-translational modifications were investigated by peptide mapping. The level of deamidation was confirmed to be comparable. In addition, the level of methionine oxidation was sufficiently demonstrated to be similar between MSB11456 batches and RMP.

The level of glycation was demonstrated to differ significantly between MSB11456 and the RMP, in that the levels are higher for MSB11456 both in terms of total glycation and glycation for individual chains. The applicant justified these differences. The biological activity of MSB11456 and the RMP was also demonstrated to be similar, see the following section. In addition, a thorough evaluation of the structure-function relationship is presented in section 3.2.R.1.5.6. In conclusion, it is found sufficiently justified that the efficacy is not influenced by the slightly higher level of glycation observed for the RMP.

N- and C-terminal variants were investigated by peptide mapping and Edman sequencing and the same N- and C-terminal variants were identified for MSB11456 and the RMP. The levels were sufficiently similar, with slight shifts observed that are not likely to influence efficiency or safety.

Overall, similar primary structure and post-translational modifications have at large been demonstrated for batches of the biosimilar candidate, MSB11456 FP-IV (vial) and FP-SC (PFS), to the EU approved RoActemra (RMP) and US approved Actemra (RP).

It can also be concluded that the EU-approved RoActemra (RMP) and US-approved Actemra are considered comparable with respect to primary structure and PTMs.

Higher order structure

The secondary structure of MSB11456 finished product was demonstrated to be similar to RMP and RP by FTIR and far-UV-CD. Tertiary structure was demonstrated to be similar by near UV-CD and fluorescence scan spectroscopy.

The levels of free thiols were determined to be consistently low, and the position of disulfide bonds were confirmed for all three products.

In conclusion, the analyses included in the study and the obtained results sufficiently demonstrate that the higher order structure of MSB11456 is similar to that of the RMP, for both the PFS and the vial presentations. It can also be concluded that the EU-approved RoActemra (RMP) and US-approved Actemra are considered comparable with respect to higher order structure.

Purity and impurities

Several complementary and orthogonal analytical tests have been applied to compare batches of the biosimilar candidate, MSB11456 FP-IV (vial) and FP-SC (PFS), to the EU approved RoActemra (RMP) and US approved Actemra (RP) for SC or IV use with respect to purity and impurities. This comparison includes assessment of monomer content and HMW forms (dimer and higher aggregates) by SE-HPLC, AUC and SE-HPLCMALLS, as well as determination of purity by CE-SDS and sub-visible particles by LO and MFI.

The chromatograms for SE-HPLC show similar size variant profiles for both the MSB11456 vial (FP-IV) and PFS (FP-SC) compared to RoActemra and Actemra. The level of HMWs as determined by SE-HPLC is in general found low for all products studied and the FP-IV batches have slightly lower levels of HMWs than the corresponding RMP and RP. The applicant considers this difference as positive for the biosimilar candidate and this is agreed to.

Similar monomeric purity, dimer and higher aggregate levels have been demonstrated by AUC for both the MSB11456 vial (FP-IV) and PFS (FP-SC) compared to RoActemra and Actemra. Similar monomer molecular weight has been demonstrated by SE-HPLC MALLS for both the MSB11456 vial (FP-IV) and PFS (FP-SC) compared to RoActemra and Actemra.

The CE-SDS electropherograms show that all products studied contain the same species. The applicant considers this slight difference as positive for the biosimilar candidate and this is agreed to.

The levels of SVP as determined by LO and MFI are found comparable or slightly lower for the MSB11456 vial (FP-IV) and PFS (FP-SC) compared to RoActemra and Actemra. The levels are also found well within the limits as defined in Ph. Eur. 2.9.19.

In conclusion, the assessment of monomer content and HMW/LMW forms by SE-HPLC, AUC and SE-HPLC-MALLS, and determination of purity and LMW species by CE-SDS and sub-visible particles by LO and MFI all support the biosimilarity claim for the MSB11456 vial (FP-IV) and PFS (FP-SC) compared to the RMP RoActemra and RP Actemra. It can also be concluded that the EU-approved RoActemra (RMP) and US-approved Actemra are considered comparable with respect to the analysis of purity and impurities.

Product variants

This section on product variants provides a summary of data to demonstrate similarity for batches of the biosimilar candidate, MSB11456 FP-IV (vial) and FP-SC (PFS), to the EU approved RoActemra

(RMP) and US approved Actemra (RP) with respect to charge, oxidation, sialic acids and glycan variants.

The analysis of charge variants profile for similarity was performed by using IEX-HPLC and an orthogonal icIEF method.

IEX-HPLC show highly similar charge variants profile for batches of the biosimilar candidate, MSB11456 FP-IV (vial) and FP-SC (PFS), to the EU approved RoActemra (RMP) and US approved Actemra (RP). A somewhat lower/higher level of acidic and/or basic variants is noted for the MSB11456 FP-IV (vial) and FP-SC (PFS) compared to the RMP and RP. The applicant argues that this difference is minor and not expected to be clinically meaningful. This is agreed to.

icIEF show similar levels of acidic, basic and main peaks although the levels of basic peaks are slighly lower for MSB11456 FP-SC (PFS) compared to the batches of RMP RoActemra and RP Actemra.

RP-UPLCwas employed to assess oxidised product variants. This analysis shows similar levels in oxidation for batches of the biosimilar candidate, MSB11456 FP-IV (vial) and FP-SC (PFS), to the EU approved RoActemra (RMP) and US approved Actemra (RP). A minor difference is noted between the MSB11456 FP-SC and US-approved Actemra (RP), however, the applicant argues that this minor difference is highly unlikely to be clinically meaningful and this is agreed to.

Sialic acid analysis by HPAEC-PAD demonstrated that MSB11456 and the RMP and RP have similar, very low levels of sialic acid capped glycans.

Glycan mapping by 2AB was performed to compare the glycosylation profile between MSB11456 and the RMP/RP. The patterns are similar. The applicant justifies that the observed difference in galactosylation is not expected to impact biological activities *in vivo*. The justification is found acceptable.

In conclusion, similar charge variants profile, oxidised variants and sialic acids have at large been demonstrated for batches of the biosimilar candidate, MSB11456 FP-IV (vial) and FP-SC (PFS), to the EU approved RoActemra (RMP) and US approved Actemra (RP). The minor differences noted in charge variants profile have been sufficiently justified as not clinically meaningful. The differences in formulations between the biosimilar candidate FP-IV and FP-SC to the RMP RoActemra and RP Actemra seem only to have a minor impact on charge variants and level of oxidised species.

It can also be concluded that the EU-approved RoActemra (RMP) and US-approved Actemra are considered comparable with respect to the analysis of charge, oxidation and sialic acids.

Analytical biosimilarity with respect to glycan groups is found demonstrated. In addition, it can be concluded that the EU-approved RoActemra (RMP) and US-approved Actemra are considered comparable with respect to glycan groups.

Biological characterisation

The methods used to for characterisation of biological activity can be divided into four categories, i.e. those measuring Fab binding, intracellular signalling activity, Fc binding and Fc effector function, respectively. The methods are sufficiently described in the dossier.

Fab binding is tested by different assays. For both vial and PFS it is demonstrated that Fab binding and inhibition of IL-6 activity of MSB11456 is similar as compared to EU-RMP and the US-RP. This is found acceptable.

Several analytical tests have been applied to compare MSB11456, EU-RMP and US-RP with respect to Fc-related bioactivity. Binding towards FcRn, FcγR was evaluated by SPR methods and C1q was evaluated by ELISA. Data from the analyses is presented both graphically and in tabular form. The

results sufficiently demonstrate that Fc binding of MSB11456 is similar to EU-RMP and US-RP, for both the PFS and the vial presentations. This is found acceptable.

Antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) were evaluated since these effector functions cannot be excluded as potentially contributing to the biological activities of an IgG1 antibody directed against a membrane bound target. The results sufficiently demonstrate lack of ADCC and CDC for MSB11456, EU-RMP and US-RP.

A few additional *in vitro* pharmacodynamic studies were performed to complement the Fab, Fc binding and effector function assays for both the PFS and vial presentations. The results further support the biosimilarity claim with respect to biological activity.

In conclusion, the methods used for biological characterisation are found relevant and appropriately described. The results confirmed that the biosimilar candidate, MSB11456 FP-IV (vial) and FP-SC (PFS), is similar to the EU approved RoActemra (RMP) and US approved Actemra (RP) with respect to biological activity. It can also be concluded that the EU-approved RoActemra (RMP) and US-approved Actemra are considered comparable.

Comparative forced degradation stability study

The results from comparative forced degradation stability studies of the biosimilar candidate, MSB11456 FP-IV (vial, all three volumes) and FP-SC (PFS), to the EU approved RoActemra (RMP) and US approved Actemra (RP) are provided in section 3.2.P.8.3 but are assessed in the Analytical similarity section in 3.2.R.1.

In conclusion, the results from the comparative forced degradation stability studies demonstrate similar degradation rates and pathways for the biosimilar candidate, MSB11456 FP-IV (vial) and FP-SC (PFS), to the EU approved RoActemra (RMP) and US approved Actemra (RP). Furthermore, additional data from comparative variant characterisation studies of the impact of oxidation, charge and size variants and glycation on biological activities show that the minor differences seen between MSB11456 FP-IV (vial) and FP-SC (PFS) to RoActemra and Actemra have no effect on binding and potency. The comparison in the comparative forced degradation study supports the claim for biosimilarity.

It can also be concluded that the EU-approved RoActemra and US-approved Actemra are considered comparable with respect to the results provided in the comparative forced degradation stability studies.

2.4.4.1. Adventitious agents

The origin of the CHO cell line, the pre-MCB and the MCB-1, WCB-1.1 and the ExCB-1.1.2 (extended cultivation) have all been described adequately in their history and manufacture.

There are no animal derived components used in the active substance upstream or downstream processes or in the finished product formulation. All raw materials are certified to be free of animal derived components based on supplier certificates and a BSE/TSE declaration.

The MCB-1, WCB-1.1 and ExCB-1.1.2 were all tested negative.

The testing of future WCBs is found appropriate. The necessity to perform *in vivo* tests for the qualification of future WCBs was removed by the applicant in line with 3R recommendation.

Model viruses were used in the virus clearance studies. The extent and type of viruses used with their different characteristics of genome, size and enveloped or non-enveloped are endorsed.

The selection of steps studied and the rationale for the chosen parameters used during the scale-down studies are justified and further described. Some further information on the use of controls was asked for and provided.

A risk assessment with a discussion on CPPs for viral clearance has been provided and study conditions for all steps were discussed. Where a worst case setting for a parameter could not be identified, set points were used. This is accepted.

In summary, the applicant has provided the history and testing of the cell substrates and demonstrated control over the materials used in their development and also the materials used in the manufacturing process. The testing and demonstrated clearance capacity of different viruses of the manufacturing process is found sufficient. It is agreed that tocilizumab is safe from adventitious agents and TSE.

2.4.5. Discussion on chemical, pharmaceutical and biological aspects

The Tyenne dossier is overall of good quality and no major objections related to quality aspects have been raised. Information on development, manufacture and control of active substance and finished product has been presented in a satisfactory way. The results of tests carried out indicate that the active substance and finished product is manufactured in a validated and well-controlled process.

The applicant has analysed the similarity between the biosimilar candidate MSB11456 and EU approved RoActemra in a comprehensive comparability exercise.

In general, Tyenne is considered to be similar to the EU approved RoActemra at the quality level. Some minor differences are noted but the applicant justifies all minor differences as being not clinically meaningful. This is acceptable.

2.4.6. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Tyenne 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 Tyenne is considered approvable from the quality point of view.

2.4.7. 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 recommends further points for investigation.

2.5. Non-clinical aspects

2.5.1. Introduction

The active substance of MSB111456 and RoActemra is tocilizumab, a recombinant humanised immunoglobulin G1 (IgG1) monoclonal antibody directed against human interleukin 6 (IL-6) receptors (IL-6R) and is produced in Chinese Hamster Ovary cells. Tocilizumab specifically binds to the IL-6 binding site of both soluble IL-6R (sIL-6R) and membrane-bound IL-6R (mIL-6R) with similar affinity, preventing IL-6 binding to both receptors and thereby blocking the activity of IL-6. Consequently, IL-6-driven cellular functions are down-regulated.

The Non-clinical programme was focused on primary pharmacodynamics (PD). A series of *in vitro* PD studies was performed to assess any potential differences in biological activity between MSB11456 and the reference products RoActemra (EU) or Actemra (US). Given that MSB11456 is developed as a proposed biosimilar, secondary PD, safety pharmacology and PD drug interaction, PK/toxicokinetic (TK), or relevant toxicology studies were not deemed necessary, which is in accordance with EMA guideline [EMA/CHMP/BMWP/403543/2010].

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

For the non-clinical evaluation of MSB11456, a series of comparative *in vitro* studies to evaluate similarity between MSB11456 and RoActemra (EU) or Actemra (US) was conducted.

The *in vitro* pharmacological properties of MSB11456 were investigated using binding and functional assays, taking into consideration that tocilizumab is a monoclonal antibody of the IgG1 subclass that binds to the Interleukin-6 receptor (IL-6R). The *in vitro* PD activity of MSB11456 was compared with multiple batches of the reference products.

The *in vitro* assessment of binding and function included *in vitro* pharmacodynamics assays regarding Fab-dependent biological activities, Fc binding activities, Fc effector function characterisation and the supportive IL-6 induced and sIL-6R driven *in vitro* signalling assays.

Table 2 In vitro assessments

Attribute	Analytical Technique	Aim of the test
Biological Activity Attributes		
Fab binding and potency	IL-6 inhibition by in vitro bioassay*	Inhibition of IL-6-induced cell proliferation (%EC_{50})
	sIL-6R binding by SPR	Affinity to sIL-6R (KD)
	mIL-6R binding by flow cytometry	Binding to mIL-6R (%EC_{50})
Fc binding	FcRn binding by SPR	Affinity to FcRn (KD)
	FcγRI binding by SPR	Affinity to FcγRI (KD)
	FcγRII binding by SPR	Affinity to FcγRIIa R131 & H131 (KD)
	FcγRIIIa binding by SPR	Affinity to FcγRIIIa V158 & F158 (KD)
	FcγRIIIb binding by SPR	Affinity to FcγRIIIb (KD)
	C1q binding by ELISA	Binding to C1q (%EC_{50})
***In vitro* signaling activity**		
Other assays in support of similarity and extrapolation of indications	IL-6 induced signalling by flow cytometry	Inhibition of IL-6-induced signalling (%EC_{50})
	sIL-6R driven signalling by luminescence	Inhibition of sIL-6R driven signalling (%EC_{50})
Comparative *in vitro* pharmacodynamic studies to evaluate potential biological activities		
Fc-dependent effector activity	NK (V/V) ADCC-induced cell viability reduction by luminescence	ADCC with NK effector cells and target cells expressing mIL-6R (Lack of activity)
	CDC-induced cell viability reduction by luminescence	CDC with target cells expressing mIL-6R (Lack of activity)
Fab-dependent monocyte apoptosis	Apoptosis of monocytic cells by luminescence	Apoptosis of monocytic cells (Lack of activity)

The functional *in vitro* data package is deemed adequate for demonstrating the similar biological activity of MSB11456 and RoActemra or Actemra and reflects the principal mode of actions of Tocilizumab. These studies were included under Module 3 and are presented in more detailed and reviewed under Quality/Biosimilarity section.

2.5.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were performed given that there were no residual uncertainties in the comparative analytical similarity assessment and that absence of secondary pharmacodynamics studies is in alignment with regulatory guidance for biosimilar development (EMA/CHMP/BMWP/403543/2010).

2.5.2.3. Safety pharmacology programme

No safety pharmacology studies were conducted given that omission of these studies is in line with regulatory guidance for biosimilar development (EMA/CHMP/BMWP/403543/2010).

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted given that omission of these studies is in line with regulatory guidance for biosimilar development (EMA/CHMP/BMWP/403543/2010).

2.5.3. Pharmacokinetics

Comparative *in vivo* pharmacokinetic (PK)/toxicokinetic (TK) studies with MSB11456 and RoActemra or Actemra were not conducted and are not required. No differences were noted also in *in vitro* binding to FcRn between MSB11456 and RoActemra or Actemra.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Single-dose toxicity studies were not conducted given that there was no residual uncertainty in comparative analytical similarity assessment and that absence of single-dose toxicity studies is in alignment with regulatory guidance for biosimilar development (EMA/CHMP/BMWP/403543/2010).

2.5.4.2. Repeat dose toxicity

Repeat-dose toxicity studies were not conducted given that there was no residual uncertainty in comparative analytical similarity assessment and that absence of repeat-dose toxicity studies is in alignment with regulatory guidance for biosimilar development (EMA/CHMP/BMWP/403543/2010).

2.5.4.3. Genotoxicity

Genotoxicity studies were not conducted in alignment with regulatory guidance for biosimilar development (EMA/CHMP/BMWP/403543/2010).

2.5.4.4. Carcinogenicity

Carcinogenicity studies were not conducted in alignment with regulatory guidance for biosimilar development (EMA/CHMP/BMWP/403543/2010) and given that there was no residual uncertainty in comparative analytical similarity assessment.

2.5.4.5. Reproductive and developmental toxicity

Reproductive and developmental toxicity studies were not conducted in alignment with regulatory guidance for biosimilar development (EMA/CHMP/BMWP/403543/2010) and given that there was no residual uncertainty in comparative analytical similarity assessment.

2.5.4.6. Toxicokinetic data

N/A

2.5.4.7. Local tolerance

Local tolerance studies were not conducted in alignment with regulatory guidance for biosimilar development (EMA/CHMP/BMWP/403543/2010).

2.5.4.8. Other toxicity studies

No studies on other adverse effects were conducted as they are not required for a proposed biosimilar product according to the relevant guidance for biosimilars (EMA/CHMP/BMWP/403543/2010).

2.5.5. Ecotoxicity/environmental risk assessment

The active substance (MSB111456, tocilizumab) is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, MSB111456 is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

The nonclinical data package was focused on comprehensive *in vitro* functional activity analyses relevant for tocilizumab mechanism of action. No *in vivo* pharmacology, PK/TK, or toxicology studies were conducted as they are not generally required for a biosimilar for the approval of the marketing authorisation within EU.

The *in vitro* assessment of binding and function included *in vitro* pharmacodynamics assays regarding Fab-dependent biological activities, Fc binding activities, Fc effector function characterisation and the supportive assays (concerning IL-6 induced STAT3 phosphorylation, sIL-6R driven STAT3 signalling). The functional *in vitro* data package is deemed adequate for demonstrating the similar biological activity of MSB11456 and RoActemra or Actemra for both the SC and IV presentation and reflects the principal mode of actions of tocilizumab. Please refer to section 2.4 of this report.

Adequate justification for absence of the environmental risk assessment (ERA) has been provided. Monoclonal antibodies are unlikely to pose a significant risk to the environment. ERA studies are therefore not required in accordance with EMEA/CHMP/SWP/4447/00.

The active substance (MSB111456, tocilizumab) is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, MSB111456 is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The nonclinical *in vitro* functional activity data support the biosimilarity of MSB111456 versus RoActemra-EU (and or Actemra-US) for both the SC and IV presentation.

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**

Study number (CSR location)	Main Objectives	Study design Study start / Completion date	Test product Dosage/regimen Route of administration	Study population	No. of subjects treated	Study duration
Therapeutic Equivalence Study in Patients						
FKS456-001 (refer to Module 5.3.5.1)	Primary: to demonstrate equivalent efficacy of MSB11456 and EU-RoActemra Secondary: to compare safety, immunogenicity and long-term efficacy of MSB11456 and EU-RoActemra Exploratory: to explore the effect of a single treatment switch on efficacy, safety, and immunogenicity and to describe PK parameters of MSB11456 and EU-RoActemra	Multicenter, randomized (1:1), double-blind, active-controlled, multiple fixed-dose, two-arm, parallel-group study At Week 24, subjects treated with EU-RoActemra were re-randomized 1:1 to MSB11456 or EU-RoActemra. Start Date: 03 Aug 2020 Completion Date: 06 Jun 2022	Test product MSB11456 Reference product EU-RoActemra 162 mg once weekly PFS for SC injection	Adult male and female subjects ≥18 years old with moderately to severely active RA, inadequate response to therapy with at least one DMARD and on a stable dose of MTX	Randomized: 604 subjects Core Treatment Period: MSB11456: 302; EU-RoActemra: 302 Extended Treatment Period: MSB11456: 266 EU-RoActemra to MSB11456: 139 EU-RoActemra: 136 Overall Period – Including Safety Follow-up Period: MSB11456: 302; EU-RoActemra to MSB11456: 139; EU-RoActemra: 163	Screening up to 28 days Core Treatment Period: 24 weeks Extended Treatment Period: 28 weeks Safety Follow-up Period: 12 weeks Treatment duration: 51 weeks Trial duration: up to 63 weeks

Study number (CSR location)	Main Objectives	Study design Study start / Completion date	Test product Dosage/regimen Route of administration	Study population	No. of subjects treated	Study duration
Subcutaneous bioequivalence						
MS200740-0001 (refer to Module 5.3.3.1)	Primary: to demonstrate equivalence of MSB11456 to both US-Actemra and EU-RoActemra in terms of PK Secondary: - To compare the PK and PD profiles of MSB11456 to US-Actemra and EU-RoActemra - To assess and compare the immunogenicity of MSB11456 to US-Actemra and EU-RoActemra - To assess and compare the safety and tolerability of MSB11456 to US-Actemra and EU-RoActemra	Randomized (1:1:1), double-blind, parallel group, single dose study Start Date: 27 Nov 2017 Completion Date: 30 Sep 2019	Test product MSB11456 Reference products US-Actemra, EU-RoActemra Single dose of 162 mg PFS for SC injection	Healthy adult male and female subjects ≥18 to ≤55 years, body weight ≥60 to ≤100 kg	Randomized: 695 subjects No. of subjects dosed (single dose): MSB11456: 231; US-Actemra: 229; EU-RoActemra: 225	Single dose, subjects were followed up for 48 days
Intravenous bioequivalence						
FK456-002 (refer to Module 5.3.3.1)	Primary: to demonstrate PK equivalence of MSB11456 to US-Actemra after a single IV infusion in healthy subjects Secondary: to compare the safety, tolerability, and immunogenicity of MSB11456 to US-Actemra in healthy subjects	Randomized (1:1), double-blind, 2-arm, parallel group, single-dose study Start Date: 24 Sep 2020 Completion Date: 29 Jan 2021	Test product MSB11456 Reference product US-Actemra 8 mg/kg body weight IV infusion for 1 h	Healthy male and female subjects ≥18 to ≤55 years Body weight: ≥60 to ≤100 kg	Randomized: 130 subjects No. of subjects dosed (single dose): MSB11456: 62; US-Actemra: 66	Single dose, subjects were followed up for 48 days

Study number (CSR location)	Main Objectives	Study design Study start / Completion date	Test product Dosage/regimen Route of administration	Study population	No. of subjects treated	Study duration
Pre-filled syringe vs auto-injector						
FK456-003 (refer to Module 5.3.3.1)	Primary: to demonstrate PK equivalence of PFS and AI presentations of MSB11456 after SC administration in healthy subjects. Secondary: to compare the safety, and tolerability of PFS and AI presentations of MSB11456 in healthy subjects.	Randomized (1:1), open-label, single fixed dose, 2-treatment, 2-period, cross-over study with a washout period of 42 days between treatments Start Date: 26 Feb 2021 Completion Date: 12 Jun 2021	Treatment A MSB11456 PFS Treatment B MSB11456 AI Treatment sequences A-B B-A Single dose of 162 mg PFS for SC injection	Healthy male and female subjects ≥18 to ≤55 years Body weight: ≥60 to ≤100 kg	Number of randomized subjects:100 Treatment sequence A-B: 51 Treatment sequence B-A: 49 No. of subjects dosed (single dose): 100	Screening period up to 28 days. Single dose on Day 1 with follow-up to Day 43 in both treatment periods. The total duration was up to 113 days.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The clinical development programme included four clinical studies to evaluate the similarity between MSB11456 and the reference product (EU-RoActemra/US-Actemra), in terms of clinical pharmacology, efficacy, tolerability and safety.

One pivotal comparative efficacy and safety Study FKS456-001 was conducted to compare the efficacy and safety of MSB11456 with EU-RoActemra after multiple fixed-dose SC administrations in patients with rheumatoid arthritis. PK trough concentration samples were collected from all study patients at scheduled visits.

Two comparative clinical PK studies were conducted to demonstrate PK comparability and similarity between MSB11456 and EU-RoActemra/US-Actemra:

- Pivotal 3-way comparative PK Study MS200740-0001: MSB11456 versus EU-RoActemra and versus US-Actemra after single SC administration in healthy subjects.
- Pivotal 2-way comparative PK Study FKS456-002: MSB11456 versus US-Actemra after single IV infusion in healthy subjects.

In addition, a supportive 2-way comparative PK Study FKS456-003 was conducted to demonstrate equivalence of the PK profile of MSB11456 administered by either an AI or a PFS after a single SC injection of 162 mg in healthy subjects, respectively.

Immunogenicity was also evaluated in the clinical studies except for Study FKS456-003.

Analytical methods

Quantification of tocilizumab in human serum

Quantification of tocilizumab in serum of healthy and RA patients was performed using an electrochemiluminescence (ECL) immunoassay.

High bind 96-well MSD plates are coated with anti-idiotypic (Fab monovalent) antibody overnight to capture free tocilizumab and then blocked. The tocilizumab calibrators/QCs and samples are added to the plate and incubated. After washing to remove excess unbound molecules, wells are incubated with ruthenylated full immunoglobulin (Ig), and the plate is incubated for formation of bridge. After final wash steps, the read buffer is added to the plate, and the plate is read with MSD reader to obtain raw responses.

The first method developed had a wide calibration range from 103 ng/mL to 134000 ng/mL. This method was validated for sample analysis in healthy subjects. However, the method failed the 3-month long-term stability evaluation due to a high variability at the highest concentrations of the calibration curve. An investigation was initiated and a revised method with a shortened quantitation range (from 100 to 50 000 ng/mL) but otherwise identical was tested and validated.

Immunogenicity

A multi-tiered approach to detect anti-drug antibodies (ADA) and neutralising antibodies (NAb) was applied. The same validated homogeneous electrochemiluminescence (ECL) bridging format incorporating an acid-dissociation sample pre-treatment step was applied for testing of samples from all three clinical studies, with minor changes to operating conditions.

A cell-based assay dependent on the biological activity of hIL-6 was used to detect neutralising antibodies to tocilizumab. The cell-based NAb assay measures a luminescence signal induced by binding of rhIL-6 to IL-6 receptors (IL-6R) expressed on the surface of the Promega SIE-luc2p/HEK293 cell line. MSB11456 binds to IL-6R, inhibiting the binding of IL-6 to IL-6R and thereby reducing IL-6-mediated signal transduction and luciferase activity. Anti-tocilizumab NAb binds to MB11456 to enable IL-6 to bind to its receptor and activate signaling pathway to increase luciferase activity and the luminescence signal.

PK studies

The pivotal data for demonstrating PK similarity with the reference product are obtained from two single-dose studies in healthy subjects: Study MS200740-0001 (single-dose 162 mg SC injection) and Study FKS456-002 (single-dose 8 mg/kg IV infusion).

Study MS200740-0001 (single-dose SC injection):

This study was a randomised, double-blind, parallel group, single-dose study to compare PK, PD, safety, tolerability and immunogenicity of MSB11456 versus US-Actemra and EU-RoActemra in healthy adult subjects.

A single dose of 162 mg of MSB11456, US-Actemra or EU-RoActemra was administered as a subcutaneous injection in the lower abdomen.

Subjects were randomised in a 1:1:1 ratio stratified by weight category (≥ 60 and ≤ 80 kg, > 80 and ≤ 100 kg).

Overall, 685 subjects received one single dose of MSB11456 (231 subjects), US-Actemra (229) or EU-RoActemra (225 subjects) as a SC injection of 162 mg. Of the 685 subjects who received treatment and were included in the Safety Analysis set; 680 subjects (99.3%) were included in the PK Analysis set and 666 subjects (97.2%) completed the study.

Sample sise re-estimation: Initially, 318 subjects were planned to be randomised (106 subjects per arm). A blinded sample re-estimation (BSSR) was conducted after 163 subjects completed the study up to Day 29, resulting in an increase of the sample size to up to 696 subjects.

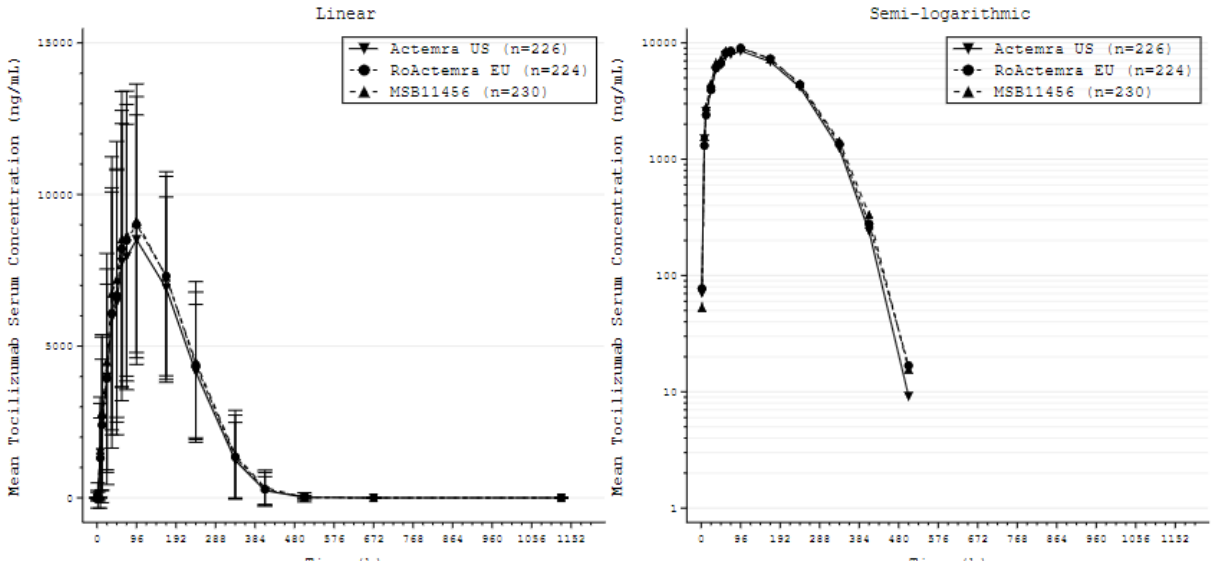
The primary PK endpoints were $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}.

PK results:

The mean tocilizumab concentrations over time for all 3 treatment arms are depicted in Figure 2.

Following a single subcutaneous administration, mean tocilizumab serum concentrations increased rapidly and reached peak concentrations on Day 4 (96 hours) post-dose in all 3 treatments. Mean tocilizumab serum concentrations declined in a multi-exponential manner, with the last mean concentration above the LLOQ observed on Day 22 (504 hours) in all 3 treatments. Overall, the mean PK profiles were very similar and mostly overlapping among the 3 treatments.

Figure 2 Arithmetic mean (±SD) tocilizumab serum concentration-time profiles for all treatments on linear and semi logarithmic scales - PK Analysis Set



The descriptive statistics for PK parameters by treatment group are presented in Table 3.

Overall, the PK parameters were similar between MSB11456 and the reference products.

Table 3 Descriptive statistics for tocilizumab serum pharmacokinetic parameters for each treatment - PK Analysis Set

	Geometric Mean (GCV%)					
	MSB11456		Actemra US		RoActemra EU	
Parameter	**n**	**Estimates**	**n**	**Estimates**	**n**	**Estimates**
$AUC_{0-\infty}$ (µg·h/mL)	194	1890 (72.9)	190	1790 (55.3)	200	1790 (58.3)
AUC_{0-t} (µg·h/mL)	230	1490 (104.8)	226	1460 (78.6)	224	1560 (75.9)
AUC_{0-72} (µg·h/mL)	229	298 (121.3)	225	279 (98.7)	224	297 (90.8)
C_{max} (µg/mL)	230	7.89 (84.2)	226	7.68 (67.1)	224	8.26 (63.6)
t_{max} (h) [a]	230	96.00 (36.00 – 240.00)	226	96.00 (36.00 – 240.15)	224	96.00 (36.00 – 196.90)
t_{last} (h)[a]	230	406.49 (167.53 – 505.07)	226	405.88 (236.58 – 504.13)	224	406.48 (168.00 – 505.00)
CL/F (L/h)	194	0.0859 (72.9)	190	0.0903 (55.3)	200	0.0904 (58.3)
$t_{1/2}$ (h)	194	43.0 (30.7)	190	43.3 (27.0)	200	42.8 (27.1)

Source: Table 15.4.2.1

GCV% = geometric coefficient of variation.

[a] Presented as median (minimum - maximum).

The statistical analysis results for the primary objectives to demonstrate PK similarity are presented in Table 4.

For all primary PK parameters ($AUC_{0-\infty}$, AUC_{0-t}, and C_{max}) and all pairwise treatment comparisons (MSB11456 versus US-Actemra; MSB11456 versus EU-RoActemra; and US-Actemra versus EU-RoActemra), the 90% CIs for the geometric LS mean ratio were contained within the predefined 80.00% to 125.00% similarity margin.

The results from the primary PK analysis demonstrated PK similarity between MSB11456 and the reference products (EU-RoActemra and US-Actemra) as well as between the reference products.

Table 4 Statistical analysis results - PK Analysis Set

Comparison	Parameter	Treatment	n	Geo LS Mean	Ratio (%)	90% CI of Ratio
MSB11456 versus Actemra US	$AUC_{0-\infty}$ (µg·h/mL)	MSB11456	194	1880	106.16	(96.80, 116.43)
		Actemra US	190	1770		
	AUC_{0-t} (µg·h/mL)	MSB11456	230	1470	104.15	(93.58, 115.90)
		Actemra US	226	1410		
	C_{max} (µg/mL)	MSB11456	230	7.91	104.45	(95.05, 114.77)
		Actemra US	226	7.57		
MSB11456 versus RoActemra EU	$AUC_{0-\infty}$ (µg·h/mL)	MSB11456	194	1880	104.03	(94.96, 113.96)
		RoActemra EU	200	1810		
	AUC_{0-t} (µg·h/mL)	MSB11456	230	1470	94.78	(85.15, 105.50)
		RoActemra EU	224	1550		
	C_{max} (µg/mL)	MSB11456	230	7.91	94.83	(86.28, 104.22)
		RoActemra EU	224	8.34		
Actemra US versus RoActemra EU	$AUC_{0-\infty}$ (µg·h/mL)	Actemra US	190	1770	97.99	(89.40, 107.41)
		RoActemra EU	200	1810		
	AUC_{0-t} (µg·h/mL)	Actemra US	226	1410	91.01	(81.71, 101.36)
		RoActemra EU	224	1550		
	C_{max} (µg/mL)	Actemra US	226	7.57	90.79	(82.57, 99.84)
		RoActemra EU	224	8.34		

BMI = body mass index, CI = confidence interval, eCRF = electronic Case Report Form, IWRS = Interactive Web Response System, Geo LS = geometric least-squares, PK = pharmacokinetic.

Results based on an analysis of covariance model including treatment (MSB11456, Actemra US, and RoActemra EU) as a fixed effect, baseline weight category (from IWRS, or eCRF for sentinel subjects), baseline BMI (continuous), and study center as covariates. The PK parameters were natural log-transformed prior to the analysis, then the results were transformed back to the original scale.

All PK parameters were additionally summarised by subgroups based on ADA status, NAb status, baseline weight, baseline BMI, and study centre.

Sensitivity analyses were conducted to evaluate the effects of the ANCOVA covariates, as well as PK outliers, on the statistical results, as planned in the IAP. Similarity was demonstrated between treatments for all sensitivity analyses, supporting the results from the primary analysis.

Subgroup summaries of the PK parameters showed no apparent difference in primary PK parameters among the treatments for ADA positive, ADA negative, or NAb negative subgroups; the NAb positive subgroups were too small to draw any conclusions.

For the weight and BMI categories, tocilizumab exposure was lower in the higher weight and BMI sub-groups across the 3 treatments. In the study centre comparison, exposure in Study Centre 102 appeared to be higher than that observed in Study Centre 101 in the MSB11456 treatment.

Evaluation of the impact of missing AUC_{0-inf} parameter on PK descriptive statistics: It was noted that in around 11 to 16% of subjects who participated in the study, it was not possible to calculate the terminal rate constant as described in the SAP. Consequently, the half-life and other associated parameters such as AUC_{0-inf} and clearance could not be calculated for these subjects. An analysis was undertaken to determine why these PK parameters were missing and to investigate the possible impact of these missing data on PK descriptive statistics.

Study FKS456-002 (single-dose IV infusion):

This study was a randomised, double-blind, two-arm, parallel-group, single-dose study designed to show PK similarity of MSB11456 with the reference product (US-Actemra) after a single IV infusion of 8 mg/kg for 1 hour in healthy subjects.

Subjects were randomised to receive a single IV infusion of 8 mg/kg of either MSB11456 or reference product (US-Actemra) for 1 hour.

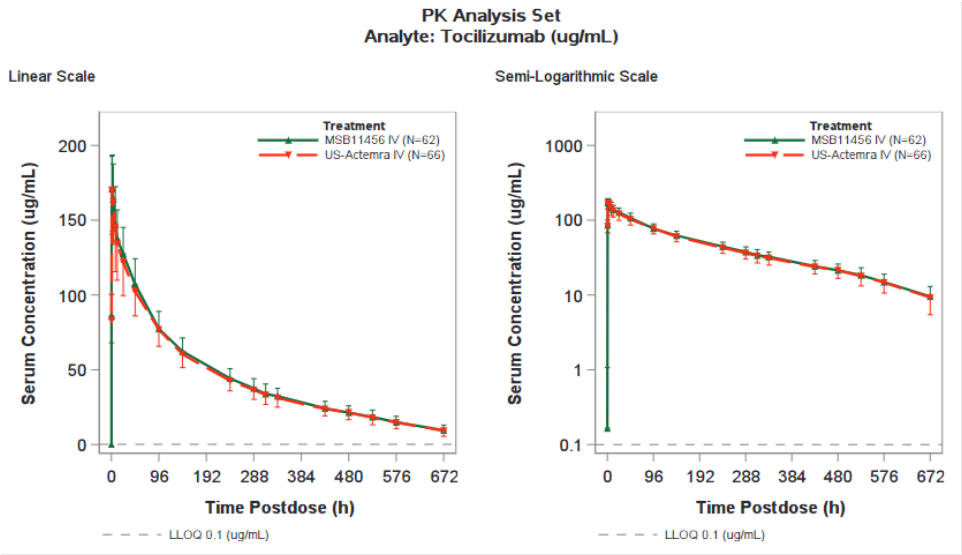
A total of 128 subjects received 1 IV dose of IMP (8 mg/kg tocilizumab), of which 62 subjects received 1 IV dose of MSB11456 and 66 subjects received 1 IV dose of reference product. All 128 subjects completed the study.

PK results:

The mean tocilizumab serum concentrations versus time are presented in Figure 3.

The overall shape of the arithmetic mean serum concentration-time profiles of tocilizumab was similar between MSB11456 and the reference product. Tocilizumab concentrations decreased gradually by a nonlinear, biphasic elimination (i.e., a combination of linear clearance and saturable elimination).

Figure 3 Plot of arithmetic mean (±SD) tocilizumab serum concentrations vs time on a linear scale and semi-logarithmic scale - PK Analysis Set



A summary of tocilizumab serum PK parameters in the PK analysis set is presented by treatment in Table 5.

Overall, the PK parameters were similar between MSB11456 and the reference product.

Table 5 Summary of tocilizumab serum PK parameters - PK Analysis Set

Treatment	Median (Range)	Geometric Mean (Geometric CV%)						
	T_{max} (h)	C_{max} (µg/mL)	$AUC_{0\text{-last}}$ (h·µg/mL)	AUC_{0-inf} (h·µg/mL)	$AUC_{\%extrap}$ (%)	λ_z (1/h)	$t^{1/2}$ (h)	CL (mL/h)
US-Actemra IV (N = 66)	2.0 (1.00-12.00)	172 (16.7%)	27926 (17.2%)	30928 (18.9%)	8.6 (64.3%)	0.00347 (20.4%)	200 (20.4%)	19.6 (18.8%)
MSB11456 IV (N = 62)	2.0 (0.78-8.02)	175 (12.2%)	28858 (15.3%)	31902 (17.2%)	8.4 (72.2%)	0.00346 (19.3%)	200 (19.3%)	19.2 (16.7%)

Source: Refer to Module 5 Section 5.3.3.1 Study Report FKS456-002, Table 14.2.2

The statistical analysis of the biosimilarity of MSB11456 versus US-Actemra for the primary PK endpoint ($AUC_{0\text{-last}}$) and secondary PK parameters (C_{max} and $AUC_{0\text{-inf}}$) is presented in Table 6.

For $AUC_{0\text{-last}}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional biosimilarity acceptance range of 80.00-125.00% when comparing MSB11456 to US-Actemra. PK similarity was additionally demonstrated for the secondary PK parameters $AUC_{0\text{-inf}}$ and C_{max}. The GMRs (and 90% Cis) were 103.34 (98.53-108.37%) for $AUC_{0\text{-last}}$, 103.15% (97.86-108.73%) for $AUC_{0\text{-inf}}$ and 101.48% (97.23-105.92%) for C_{max}.

Thus, PK similarity was demonstrated between MSB11456 and US-Actemra.

Table 6 Statistical analysis of biosimilarity of MSB11456 versus US-Actemra - PK Analysis Set

PK Analysis Set

Analyte: Tocilizumab

Parameter	MSB11456 IV (Test) (N=62) n	MSB11456 IV (Test) (N=62) GLSM (95% CI)	US-Actemra IV (Reference) (N=66) n	US-Actemra IV (Reference) (N=66) GLSM (95% CI)	Ratio (Test/Reference) GLSM (90% CI)
Cmax (ug/mL)	62	175 (168,181)	66	172 (166,178)	101.48 (97.23, 105.92)
AUC0-last (h*ug/mL)	62	28858 (27704,30060)	66	27926 (26843,29053)	103.34 (98.53, 108.37)
AUC(0-inf) (h*ug/mL)	62	31902 (30494,33376)	66	30928 (29603,32311)	103.15 (97.86, 108.73)

CI = Confidence Interval, GLSM = Geometric Least Squares Mean.
The analysis is performed on natural log (ln) transformed parameters using an analysis of variance model with treatment as a fixed effect.
Source: Listing 16.2.6.2.

Study FKS456-003 (PFS vs AI):

In addition to the pivotal PK studies, a supportive 2-way comparative PK Study FKS456-003 was conducted to demonstrate equivalence of the PK profile of MSB11456 administered by either a PFS or an AI after a single SC injection of 162 mg in healthy subjects, respectively.

Study FKS456-003 was a randomised, open-label, single fixed-dose, 2-treatment, 2-period, cross-over study in healthy male and female subjects.

A single dose of 162 mg (180 mg/mL in 0.9 mL) MSB11456 was administered as an SC injection in the lower abdomen, upper thigh, or outer area of upper arm, using a PFS or an AI.

PK results:

The statistical analysis of the equivalence of AI and PFS presentations of MSB11456 is presented in the table below.

Table 7 Statistical analysis of bioequivalence of MSB11456 AI vs MSB11456 PFS - PK Analysis Set

	Auto-injector (Test)		Prefilled Syringe (Reference)		Ratio	
	(N=91)		(N=91)		(Test/Reference)	
Parameter	**n**	**GLSM (95% CI)**	**n**	**GLSM (95% CI)**	**GLSM**	**(90% CI)**
C_{max} (µg/mL)	90	8.33 (7.34,9.45)	91	8.36 (7.37,9.47)	99.67	(90.95, 109.21)
$AUC_{0\text{-}last}$ (h·µg/mL)	90	1470 (1275,1695)	91	1429 (1240,1647)	102.88	(92.21, 114.79)
$AUC_{0\text{-}inf}$ (h·µg/mL)	88	1535 (1361,1731)	88	1532 (1358,1727)	100.23	(92.67, 108.41)

Source: Refer to Module 5 Section 5.3.3.1 Study Report FKS456-003, Table 14.2.3

CI = confidence interval, GLSM = geometric least-squares mean, IRT = interactive response technology, n = number of subjects with available data, PK = pharmacokinetics
The analyses were performed on natural logarithm-transformed parameters using an analysis of variance model, with treatment sequence, period, treatment presentation, baseline body weight strata (based on IRT), and administration site as fixed effects, and subject nested within sequence as a random effect.

For C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional bioequivalence acceptance range of 80.00-125.00% when comparing the AI to the PFS. The GMRs (and 90% CIs) were 99.67% (90.95-109.21%) for C_{max}, 102.88% (92.21-114.79%) for $AUC_{0\text{-}last}$, and 100.23% (92.67-108.41%) for $AUC_{0\text{-}inf}$.

Thus, PK equivalence was demonstrated between the PFS and AI presentations of MSB11456. Also, the secondary PK endpoints were comparable between PFS and AI presentations of MSB11456.

Pharmacokinetics in target population

Study FKS456-001 (RA patients):

PK data were obtained from the phase III study FKS456-001 in patients with RA (using EU-RoActemra). The blood samples were collected before tocilizumab administration at baseline, week 2, 3, 4, 5, 6, 7, 9, 10, 11 and 12 and end of core treatment (week 24), extended by pre-dose samples at week 30, 42 and 52.

At baseline, mean trough tocilizumab concentrations were below the limit of quantification in both the MSB11456 and EU-RoActemra groups. Steady-state was reached after 8-12 weeks. The mean trough tocilizumab concentrations in the MSB11456 and EU-RoActemra groups were sustained at week 24 of the Core Period (32058.4 ng/mL and 35442.8 ng/mL, respectively) and week 30 of the Overall Period (31005.9 ng/mL and 35478.9 ng/mL, respectively), with similar concentrations in the MSB11456 and EU-RoActemra groups.

During the Overall Period, the mean trough concentration in the EU-RoActemra-to-MSB11456 group at week 24 was maintained at week 30 (35284.7 ng/mL) and was similar to the trough concentrations in the MSB11456 and EU-RoActemra groups.

Table 8 Mean serum C_{trough} concentrations of tocilizumab up to week 24 - PK Analysis Set

Time Point	Mean (SD) Serum C_{trough} Tocilizumab Concentrations (ng/mL)	
	MSB11456 (N=302)	EU-RoActemra (N=301)
Baseline	50.0 (0.00)	67.3 (296.27)
Week 1	6808.5 (5417.97)	7004.2 (4347.80)
Week 2	12113.0 (7925.60)	13276.3 (7291.67)
Week 4	20158.5 (10947.69)	22044.8 (10643.18)
Week 8	28204.4 (15855.80)	29888.6 (16426.66)
Week 12	32375.8 (18255.03)	33456.4 (18449.98)
Week 24	32058.4 (20660.00)	35442.8 (20416.07)
Week 30 [1]	31005.9 (20601.75)	35478.9 (22458.81) [2]

Source: Refer to Module 5 Section 5.3.3.1 Study Report FKS456-001, Table 53.

[1] Source: Refer to Module 5 Section 5.3.3.1 Study Report FKS456-001, Table 14.2.8.3.3.

[2] N=163 (After partly transition to MSB11456)

Values below the lower limit of quantification (LLOQ) were imputed as ½LLOQ. Missing values due to no sample, insufficient sample volume for analysis, no result or result not valid were excluded from the analysis.

SD = standard deviation

Table 9 Mean serum C_{trough} concentrations of tocilizumab in extension period (week 24 onwards) - EP-PK Analysis Set

Time Point	Mean (SD) Serum C_{trough} Tocilizumab Concentrations (ng/mL)		
	MSB11456 (N=260)	EU-RoActemra / MSB11456 (N=134)	EU-RoActemra (N=131)
Baseline (Week 24)	33067.2 (19759.38)	34921.8 (17545.70)	38405.2 (21559.91)
Week 30	31608.2 (20338.17)	35284.7 (20697.86)	36022.6 (22193.51)

Source: Refer to Module 5 Section 5.3.3.1 Study Report FKS456-001, Table 14.2.8.3.2.

Values below the lower limit of quantification (LLOQ) were imputed as ½LLOQ. Missing values due to no sample, insufficient sample volume for analysis, no result or result not valid were excluded from the analysis.

Table 10 Trough Concentration by Time Point - Overall Period (PK Analysis Set)

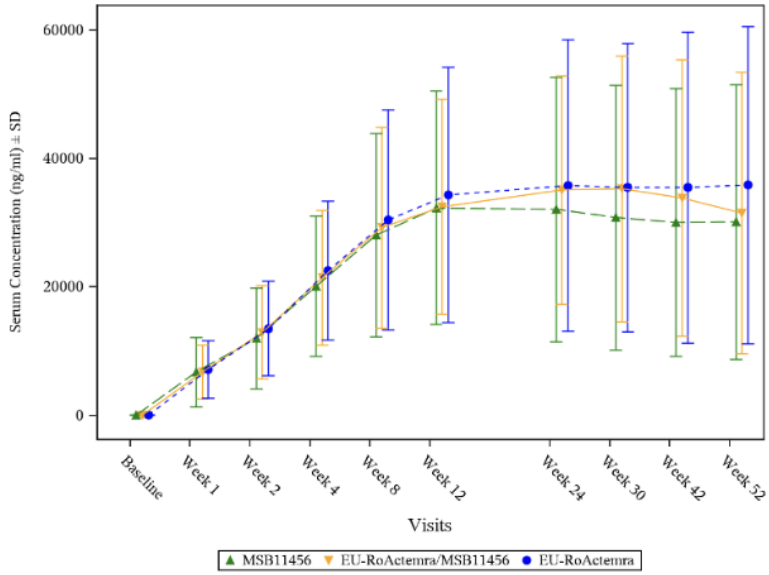
Table 14.2.8.3.3 Trough Concentration by Time Point - Overall Period
(PK Analysis Set)

Time Point Statistic (ng/mL)	MSB11456 (N=299)	EU-RoActemra/ MSB11456 (N=138)	EU-RoActemra (N=163)
Week 42			
n (missing)	256 (43)	131 (7)	132 (31)
Mean (std)	30060.5 (20841.17)	33858.8 (21547.81)	35500.7 (24213.44)
CV	69.33	63.64	68.21
Geometric Mean	14386.6	15507.0	20369.3
Geometric CV	715.65	1031.51	412.98
Median	30200.0	33200.0	32200.0
Min, Max	50, 93200	50, 90700	50, 107000
Week 52			
n (missing)	244 (55)	125 (13)	126 (37)
Mean (std)	30134.0 (21379.32)	31502.2 (21922.07)	35878.8 (24668.39)
CV	70.95	69.59	68.75
Geometric Mean	13751.8	15295.9	21899.3
Geometric CV	836.44	658.47	318.79
Median	28750.0	32000.0	30550.0
Min, Max	50, 102000	50, 85700	50, 116000

Values below the lower limit of quantification (LLOQ) will be imputed as ½LLOQ.
Missing values due to no sample, insufficient sample volume for analysis, no result or result not valid were excluded from the analysis.

Source: Listing 16.2.6.7, Dataset: ADPC, Program: t-con-pk-Over.sas, Output: T-14-02-08-03-03-con-pk-Over.rtf, Generated on: 2022-08-11T07:25, Page 5 of 5

Figure 4 Mean trough concentration over time (linear scale) – Overall Period - PK Analysis Set



Source: Refer to CSR, Figure 9 and Figure 14.3.2.1.1

Absorption

No data on absorption and bioavailability was generated specifically for MSB11456 throughout the development programme. The PK parameters indicative of rate and extent of absorption of tocilizumab after a single SC 162 mg MSB11456 dose administered via PFS in healthy subjects were fairly comparable between Study MS200740-0001 and FKS456-003.

Table 11 Inter-study comparison of MSB11456 in serum - absorption and bioavailability PK metrics

	Geometric Mean (Geometric CV%)			
	162 mg SC MSB11456 via PFS			
Study	**MS200740-0001**		**FKS456-003**	
Parameter	**n**	**Estimates**	**n**	**Estimates**
$AUC_{0\text{-}inf}$ (µg·h/mL)	194	1890 (72.9)	88	1595.3 (60)
$AUC_{0\text{-}last}$ (µg·h/mL)	230	1490 (104.8)	91	1463.3 (85)
C_{max} (µg/mL)	230	7.89 (84.2)	91	8.47 (68.2)
t_{max} (h) [a]	230	96.00 (36.00-240.00)	91	74.0 (46.4-285.5)

Source: Refer to Module 5 Section 5.3.3.1 Study Report MS200740-0001, Table 15.4.2.1 and Module 5 Section 5.3.3.1 Study Report FKS456-003, Table 14.2.2.1

Following subcutaneous dosing in RA patients, the time to peak serum RoActemra concentrations t_{max} was 2.8 days. The bioavailability for the subcutaneous formulation was 79% (RoActemra SmPC, 2021).

In adult patients with active RA, the mean steady-state Cmin concentration was 43.0 ± 19.8 µg/mL during weekly tocilizumab 162 mg treatment (RoActemra SmPC, 2021). This finding is deemed consistent with the mean trough steady-state tocilizumab concentrations of 32.1 ± 20.7 µg/mL and 35.4 ± 20.4 µg/mL, respectively, after weekly 162 mg SC injection of MSB11456 or EU-RoActemra determined in efficacy and safety Study FKS456-001.

Distribution

No data on distribution was generated specifically for MSB11456 throughout the development programme. For tocilizumab it was reported that the central volume of distribution was 3.72 L, the peripheral volume of distribution was 3.35 L resulting in a volume of distribution at steady state of 7.07 L (RoActemra SmPC, 2021).

Elimination

Regarding elimination of tocilizumab following IV administration, tocilizumab undergoes biphasic elimination from the circulation. The total clearance of tocilizumab is concentration-dependent and is the sum of the linear and non-linear clearance. The concentration-dependent non-linear clearance plays a major role at low tocilizumab concentrations. Once the non-linear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

Immunogenicity

Study MS200740-0001 (single-dose SC injection):

For ADA, 155 out of 231 subjects (67.1%) in the MSB11456 treatment; 123 out of 229 subjects (53.7%) in the US-Actemra treatment; and 148 out of 225 subjects (65.8%) in the EU-RoActemra treatment, had confirmed positive ADA test results.

PK parameters, which were similar across the three treatment groups, were not influenced by ADA positive versus ADA negative status, consistent with the relatively low treatment-emergent ADA titres detected in all three treatment groups. Thus, ADA positive status did not have an impact on PK parameters for tocilizumab in this study.

Table 12 Relationship between ADA positive vs ADA negative status and tocilizumab serum PK parameters - PK Analysis Set

Category	Parameter	Geometric Mean (GCV%)		
		MSB11456	US-Actemra	EU-RoActemra
ADA Negative	Number of subjects	76	103	77
	AUC(0-inf) µg.h/mL	1900 (68.6) [64][a]	1790 (70.5) [84][a]	1740 (64.1) [67][a]
	AUC(0-t) µg.h/mL	1370 (125.9)	1400 (93.7)	1410 (97.0)
	Cmax µg/mL	7.29 (103.6)	7.40 (79.9)	7.39 (81.1)
ADA Positive	Number of subjects	154	123	147
	AUC(0-inf) µg.h/mL	1880 (75.4) [130][a]	1800 (41.9) [106][a]	1820 (55.4) [133][a]
	AUC(0-t) µg.h/mL	1560 (94.5)	1520 (65.5)	1640 (63.8)
	Cmax µg/mL	8.21 (74.3)	7.93 (55.6)	8.76 (52.7)

ADA = anti-drug antibody, GCV% = geometric coefficient of variation.

[a] Represents parameter-specific n value.

Source: MS200740-0001 CSR Table 15.4.2.2

Study FKS456-002 (single-dose IV infusion):

Nearly all subjects had at least 1 positive ADA result after dosing (i.e., on Day 15, Day 29, and/or EOS). This incidence was similar between subjects who received MSB11456 (57 out of 62 [91.9%] subjects) and US-Actemra (65 out of 66 [98.5%] subjects). Only 1 (1.6%) subject was positive for ADA prior to dosing.

The ADA titre versus time profiles were similar across the two treatment groups; the median ADA titres were also similar and relatively low (60 to 240 depending on time point).

Table 13 Summary of tocilizumab serum PK parameters for ADA positive subjects - PK Analysis Set

PK parameter (unit)	Statistic	MSB11456 IV (N=57)	US-Actemra IV (N=65)
Cmax (µg/mL)	n	57	65
	Geo Mean (95% CI)	175 (170, 181)	171 (165, 178)
	%GeoCV	12.0	16.5
Tmax (h)	n	57	65
	Mean	1.96	2.03
	%CV	75.5	90.5
AUC0-last (h*µg/mL)	n	57	65
	Geo Mean (95% CI)	28977 (27824, 30178)	27819 (26674, 29013)
	%GeoCV	15.4	17.1
AUC0-inf (h*µg/mL)	n	57	65
	Geo Mean (95% CI)	32044 (30606, 33549)	30776 (29400, 32216)
	%GeoCV	17.4	18.6
t1/2 (h)	n	57	65
	Geo Mean (95% CI)	200 (190, 211)	199 (189, 209)
	%GeoCV	20.0	20.2
CL (mL/h)	n	57	65
	Geo Mean (95% CI)	19.1 (18.2, 19.9)	19.7 (18.8, 20.6)
	%GeoCV	17.1	18.7

Abbreviations: CV = coefficient of variation, Geo = geometric, IV = intravenous, n = number of subjects, PK = pharmacokinetics, Min = minimum, Max = maximum, SD = standard deviation

Source: FKS456-002 CSR Table 14.2.4, Listing 16.2.6.2 & Listing 16.2.6.5.

Although a higher incidence of NAb positive samples was detected in Study FKS456-002 compared with Study MS200740-0001, the NAb positive incidence was still below 10%.

The full set of PK parameters for ADA positive subjects in the MSB11456 and US-Actemra were similar; ADA negative incidence was too low to able comparison of the ADA positive versus ADA negative subpopulations in each treatment group.

Study FKS456-001 (RA patients):

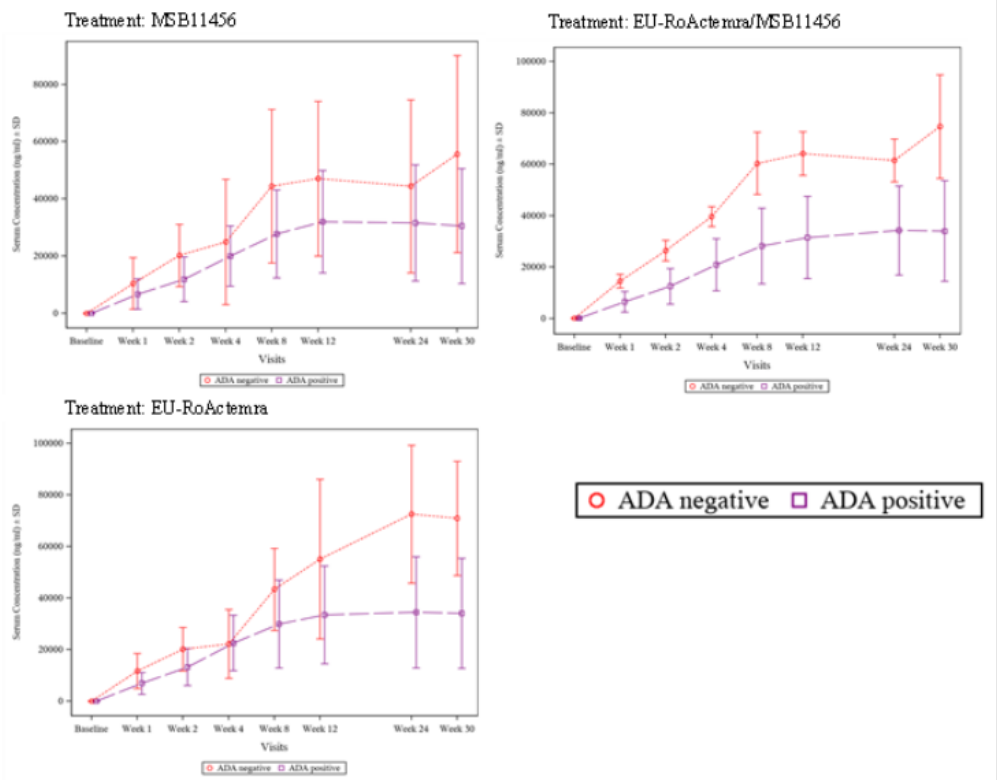
A high incidence of ADA positive results was detected in rheumatoid arthritis patients treated with MSB11456 (97% of total ADA positive patients for week 0 to week 30) and EU-RoActemra (95.7%) and 97.1% for patients who switched from EU-RoActemra to MSB11456 at week 24. ADA incidence appeared to peak at week 2 for both treatment groups.

For the majority of patients, the absolute ADA titre values were relatively low, and similar to those detected in Study FKS456-002. For the overall treatment period of 30 weeks, geometric mean ADA titre for the three treatment arms was 118.8 for MSB11456, 99.9 for EU-RoActemra and 113.1 for patients who switched from EU-RoActemra to MSB11456 at week 4. Thus, the magnitude of the ADA response to MSB11456 appeared similar to that for EU-RoActemra.

PK trough concentrations stratified by ADA status throughout the Core Period (up to week 24) and up to week 30 of the Overall Period (

Figure 5) were similar between treatment groups.

Figure 5 Mean (±SD) trough tocilizumab concentration over time (linear scale) by ADA status - Overall Period - PK Analysis Set



Source: Refer to Module 5 Section 5.3.3.1 Study Report FKS456-001, Figure 8.
EU-RoActemra/MSB11456: EU-RoActemra-to-MSB11456 group
Note: Values below the limit of quantification were imputed using the lower limit of quantification.

2.6.2.2. Pharmacodynamics

Mechanism of action

Tocilizumab is an IL-6Receptor (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 signaling through these receptors.

Study MS200740-0001 (single-dose SC injection):

This study was a randomised, double-blind, parallel-group, single-dose study to compare the PK/PD of a single 162 mg subcutaneous injection of MSB11456, US-Actemra or EU-RoActemra.

The PD parameters included: E_{max}, AUE and t_{Emax} for sIL-6R. E_{max}, AUE, t_{Emax}, E_{min} and t_{Emin} for serum CRP levels, using the high sensitivity CRP (hsCRP).

The results for sIL-6R similarity evaluation for the PD Analysis Set are presented below:

Table 14 Results for sIL-6R similarity evaluation for the PD Analysis Set

Comparison	Baseline-Adjusted Parameter	Treatment	n	Geo LS Mean	Ratio (%)	90% CI of Ratio
MSB11456 versus Actemra US	E_{max} (ng/mL)	MSB11456	230	301	102.66	(97.72, 107.86)
		Actemra US	228	293		
	AUE (ng·h/mL)	MSB11456	230	92 500	106.16	(99.18, 113.63)
		Actemra US	228	87 100		
MSB11456 versus RoActemra EU	E_{max} (ng/mL)	MSB11456	230	301	98.28	(93.53, 103.27)
		RoActemra EU	224	306		
	AUE (ng·h/mL)	MSB11456	230	92 500	97.85	(91.39, 104.76)
		RoActemra EU	224	94 500		
Actemra US versus RoActemra EU	E_{max} (ng/mL)	Actemra US	228	293	95.73	(91.09, 100.61)
		RoActemra EU	224	306		
	AUE (ng·h/mL)	Actemra US	228	87 100	92.17	(86.07, 98.71)
		RoActemra EU	224	94 500		

BMI = body mass index, CI = confidence interval, eCRF = electronic Case Report Form, IWRS = Interactive Web Response System, geo LS = geometric least-squares, PD = pharmacodynamic.
Results based on an analysis of covariance model including treatment as a fixed effect, baseline weight category (from IWRS, or eCRF for sentinel subjects), baseline BMI (continuous), and study center as covariates. The PD parameters were natural log-transformed prior to the analysis, then the results were transformed back to the original scale.

PD similarity was demonstrated for sIL-6R between MSB11456 and the reference products as well as between the reference products.

For both sIL-6R PD parameters (E_{max} and AUE) and all pairwise treatment comparisons, the 90% CIs for the geometric LS mean ratio were contained within the 80.00% to 125.00% similarity margin.

The results for CRP similarity evaluation for the PD Analysis Set are presented below:

Table 15 Results for CRP similarity evaluation for the PD Analysis Set

Comparison	Baseline-adjusted Parameter	Treatment	n	LS Mean	Difference	90% CI of Difference
MSB11456 versus Actemra US	E_{max} (µg/mL)	MSB11456	230	-1.02	-0.0989	(-0.699, 0.50)
		Actemra US	228	-0.918		
	AUE (µg·h/mL)	MSB11456	230	7.75	-77.2	(-691, 54)
		Actemra US	228	84.9		
MSB11456 versus RoActemra EU	E_{max} (µg/mL)	MSB11456	230	-1.02	0.347	(-0.255, 0.95)
		RoActemra EU	224	-1.36		
	AUE (µg·h/mL)	MSB11456	230	7.75	305	(-311, 922)
		RoActemra EU	224	-297		
Actemra US versus RoActemra EU	E_{max} (µg/mL)	Actemra US	228	-0.918	0.446	(-0.158, 1.05)
		RoActemra EU	224	-1.36		
	AUE (µg·h/mL)	Actemra US	228	84.9	382	(-237, 1000)
		RoActemra EU	224	-297		
Comparison	**Observed Parameter**	**Treatment**	**n**	**Geo LS Mean**	**Ratio (%)**	**90% CI of Ratio**
MSB11456 versus Actemra US	E_{min} (µg/mL)	MSB11456	230	0.168	93.04	(84.93, 101.92)
		Actemra US	228	0.181		
MSB11456 versus RoActemra EU	E_{min} (µg/mL)	MSB11456	230	0.168	99.17	(90.50, 108.68)
		RoActemra EU	224	0.170		
Actemra US versus RoActemra EU	E_{min} (µg/mL)	Actemra US	228	0.181	106.60	(97.24, 116.85)
		RoActemra EU	224	0.170		

BMI = body mass index, CI = confidence interval, eCRF = electronic Case Report Form, Geo = geometric, IWRS = Interactive Web Response System, LS = least-squares, PD = pharmacodynamic.

Results based on an analysis of covariance model including treatment as a fixed effect, baseline weight category (from IWRS, or eCRF for sentinel subjects), baseline BMI (continuous), and study center as covariates. For E_{min}, the data were natural log-transformed prior to the analysis, then the results were transformed back to the original scale. For E_{max} and AUE data were analyzed on the original scale.

Comparability was concluded for CRP PD parameters. Based on E_{max} and AUE, CRP exposure was comparable among the 3 treatment arms. The 90% CIs of the LS mean difference included zero for all pairwise treatment comparisons. For E_{min}, the 90% CIs of the geometric LS mean ratio were contained within the predefined 80.00% to 125.00% similarity margin in all pairwise treatment comparisons.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Bioanalytical methods

Two bioanalytical methods for quantitation of tocilizumab in human serum were developed and validated. The first method failed the 3-month long-term stability evaluation due to a high variability at the highest concentrations of the calibration curve. In the revised second method the calibration range was shortened.

Both analytical methods were used to analyse samples from the study MS200740-0001. The maximum concentration measured in the study was 24,800 ng/ml, which is below the selected upper limit of quantification (ULOQ) for the second method. It is agreed that the restriction of the calibration curve did not have an impact on sample analysis. Each PK sample from the study was analysed only with one

method, and the corresponding concentration value reported. In the study, 5331 samples were analysed with the first method and 6246 samples were analysed with the second method. It is agreed that the ISR experiments performed during method validation demonstrated that the two assays are comparable and the two set of data can be combined.

The method for the determination of soluble sIL-6R in human serum was proven to be precise and accurate over the concentration range 10.0 – 1000 ng/mL and is considered suitable for the analyses of soluble IL-6Rin human serum.

A high sensitivity CRP (hsCRP) assay was used in order to quantify CRP in serum samples as PD variable from PK/PD study MS200740-0001. The applicant provided description of the assay, assay verification, performance of the QC samples during the analysis period. All observed QC concentration were within acceptance criteria. The data provided by the applicant are considered sufficient by the CHMP.

Since the CRP parameter is expected to be low in healthy subjects at baseline, no substantial changes in CRP levels can be observed in healthy volunteers after administration of tocilizumab. Given the low relevance of this biomarker in the evaluation of the tocilizumab PD comparability in healthy subjects, the provided supporting data are sufficient.

The ADA assay is considered adequately validated for the intended purpose. Drug tolerance is considered adequate in relation to the mean drug trough concentration (approximately 35 µg tocilizumab/mL) measured at steady-state in Study FKS456-001.

The NAb assay has lower sensitivity compared to the ADA assay. As the ADA assay is considered acceptable to detect differences in immunogenicity a new NAb method is not requested.

PK studies

The pivotal data for demonstrating PK similarity with the reference medicinal product are obtained from two single-dose studies in healthy volunteers: Study MS200740-0001 (single-dose 162 mg SC injection) and Study FKS456-002 (single-dose 8 mg/kg IV infusion). In addition, a supportive 2-way comparative PK Study FKS456-003 was conducted to demonstrate equivalence of the PK profile of MSB11456 administered by either an AI or a PFS after a single SC injection of 162 mg in healthy subjects, respectively.

MS200740-0001:

The study design is satisfactory.

The subjects included in this study were to weigh between 60 and 100 kg to ensure that PK parameters between subjects were as similar as possible. In addition to including a limited range of body weights, subjects were stratified by weight category (≥ 60 and ≤ 80 kg, or > 80 and ≤ 100 kg) during randomisation and weight category was included in the statistical analyses as a covariate. This is adequate.

MSB11456 was administered at the same dose and via the same route as EU-RoActemra or US-Actemra for subcutaneous formulation. The selected dose is acceptable.

A blinded sample size re-estimation was conducted resulting in an increase of the sample size. The blinded sample re-estimation was in general supported by the CHMP in a scientific advice. The study protocol was amended (CSP Version 4.0, amendment 3) so that the total sample size could be increased up to a maximum of 696 randomised subjects to yield 220 evaluable subjects per arm (based upon 65% GeoCV and dropout rate of 5%).

The primary PK parameters included $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max}. The PK parameters are adequate.

The secondary PK parameters included AUC_{0-72}, $AUC_{extra\%}$, t_{max}, t_{last}, λ_z, $t_{½}$, and CL/F up to 48 days post-dose. Parameter AUC_{0-72} has been selected as supportive partial AUC to ensure the similar exposure of tocilizumab until the approximate appearance of maximal levels between products.

However, the Scientific Advice was given to evaluate partial AUCs (not only AUC_{0-72}) reflecting the linear and non-linear phases in in study MS200740-0001 (see EMEA/H/SA/3323/1/2016/III; CHMP answer to Question 1 c and EMA/SA/0000060099, 2021). The clearance of tocilizumab is concentration dependent and consists from 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). The applicant did not provide calculations for partials AUCs to compare portions of linear/nonlinear clearance between test and reference product due to difficulties with establishing a timeframe reflecting the linear and non-linear clearance. Taking into account that the provided studies demonstrated similarity for PK parameters after single lower dose (SC), higher dose (IV) and also for multiple doses in the treatment regimen once weekly, this issue regarding partial AUCs has not been pursued further.

For all primary PK parameters (AUC_{0-inf}, AUC_{0-t} and C_{max}) and all pairwise treatment comparisons (MSB11456 versus US-Actemra; MSB11456 versus EU-RoActemra; and US-Actemra versus EU-RoActemra), the 90% CIs for the GMRs were contained within the predefined 80.00-125.00% similarity margin.

Sensitivity analyses were conducted to evaluate the effects of the ANCOVA covariates, as well as PK outliers, on the statistical results, as planned in the IAP. Similarity was demonstrated between treatments for all sensitivity analyses, supporting the results from the primary analysis.

Also, the secondary PK endpoints were comparable between MSB11456 and the reference products.

The exclusion of subjects with missing AUC_{0-inf} values was prespecified in the protocol. Exclusion of subjects with missing AUC_{0-inf} parameter did not influence the overall study results, and tocilizumab PK remained similar across treatment groups.

FKS456-002:

The study design is satisfactory.

The applicant has previously sought CHMP advice on the development programme, and principally followed the received recommendations. As pointed in the scientific advice EMEA/H/SA/3323/1/2016/III dated 26th of May 2016, use of a non-EU licensed reference product can be acceptable as comparator in a clinical study if a comprehensive comparability exercise concerning quality characteristics, biological activity and PK equivalence study has established an acceptable bridge between the reference products. Analytical similarity studies scientifically justifying the relevance of comparative data between US-Actemra and EU-RoActemra and establish the requisite scientific bridge between these have been performed, please refer to Section 2.4. Therefore, the use of US-Actemra as a comparator in the IV PK study FK 456-002 is acceptable.

Analytical similarity studies scientifically justifying the relevance of comparative data between US-Actemra and EU-RoActemra and establishing the requisite scientific bridge between these have been performed, please refer to the section 2.4. Therefore, the use of US-Actemra as a comparator in the study is acceptable.

The chosen dose of 8 mg/kg IV infusion for 1 hour in this study reflects the current recommended maintenance dose for Actemra in adults with RA. The selected dose is acceptable.

The primary endpoint was selected to be $AUC_{0\text{-last}}$. In addition, C_{max} and $AUC_{0\text{-inf}}$ were included as standard PK endpoints. The PK parameters are adequate. The PK parameters t_{max}, λ_z, $t_{1/2}$, and CL were also measured.

For $AUC_{0\text{-last}}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional biosimilarity acceptance range of 80.00-125.00% when comparing MSB11456 to US-Actemra. PK similarity was additionally demonstrated for the secondary PK parameters $AUC_{0\text{-inf}}$ and C_{max}. The GMRs (and 90% Cis) were 103.34 (98.53-108.37%) for $AUC_{0\text{-last}}$, 103.15% (97.86-108.73%) for $AUC_{0\text{-inf}}$ and 101.48% (97.23-105.92%) for C_{max}.

Thus, PK similarity was demonstrated between MSB11456 and US-Actemra. Also, the secondary PK endpoints were comparable between AI and PFS presentations of MSB11456.

FKS456-003:

The study design is satisfactory.

The chosen dose of 162 mg MSB11456 and SC route of administration in this study is the approved dose for the tested presentations (i.e., AI and PFS), and reflect the recommended EU-RoActemra dose given weekly (or every other week) in adults with RA. This dose has also been administered to healthy subjects without posing any safety concerns. The selected dose is acceptable.

The primary parameters were $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}. The PK parameters are adequate.

For $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional bioequivalence acceptance range of 80.00-125.00% when comparing the AI to the PFS. The GMRs (and 90% CIs) were 99.67% (90.95-109.21%) for C_{max}, 102.88% (92.21-114.79%) for $AUC_{0\text{-last}}$, and 100.23% (92.67-108.41%) for $AUC_{0\text{-inf}}$.

Thus, PK equivalence was demonstrated between the AI and PFS presentations of MSB11456. Also, the secondary PK endpoints were comparable between AI and PFS presentations of MSB11456.

Elimination

In the case of tocilizumab, the total clearance is concentration-dependent and is the sum of linear (non-target mediated) clearance and nonlinear (target-mediated) clearance.

The target is also present in healthy subjects and so is target-mediated clearance but it can be a different magnitude in effect when there is more target in patients.

For MSB11456, the clearance of tocilizumab has been characterised for both doses and routes of administration in the submitted PK studies. This is in accordance with the guideline criteria. The choice of study design including choice of dose, sampling scheme and PK endpoints is adequate.

Pharmacokinetics in target population

C_{trough} is the only PK parameter in the phase 3 study. C_{trough} at different time points during the treatment can be used as a supportive PK parameter without any statistical analysis.
PK between a biosimilar product and the reference product can usually be investigated in adequately designed and conducted PK studies in healthy volunteers; supportive PK data from clinical efficacy and safety studies should usually be collected as well. As noted above, there is a pronounced target-mediated clearance for tocilizumab which could be larger in the target population. In Study FKS456-001, values below the lower limit of quantification (LLOQ) were imputed as ½LLOQ (50 ng/ml). The proportion of patients with trough concentration below LLOQ at each time point is similar for all treatment groups from baseline to week 12. It is agreed that the small numerical differences between the treatment groups are not considered to be significant. Similar mean trough concentrations

measured over the time, in particular until week 12 confirm that the target-mediated clearance is comparable between treatment arms.

A small difference in mean trough concentration is observed between the MSB11456 and EU-RoActemra arms from week 12 and onwards, and a decreased concentration is observed among patients who switch from EU-RoActemra to MSB11456 (at week 24) from week 30 and onwards. The difference in mean trough concentration may be related to the difference in ADAs from week 24 onwards.

Immunogenicity

ADAs have an impact on the PK of tocilizumab but the response was similar for MSB11456 and EU-RoActemra.

In patients given multiple doses, a small difference in mean trough concentration is observed between the MSB11456 and EU-RoActemra arms from week 12 and onwards, and a decreased concentration is observed among patients who switch from EU-RoActemra to MSB11456 (at week 24) from week 30 and onwards. The difference in mean trough concentration may be related to the difference in ADAs from week 24 onwards. The CHMP is of the opinion that this has no impact on the biosimilarity comparison.

Study FKS456-001: The incidence of treatment-induced ADA for the overall period is similar between the treatment groups, however the incidence at various timepoints is generally higher for MSB11456. Median ADA titres at week 52 are lower for the EU-RoActemra arm, compared to the MSB11456 arm. The difference in ADAs from week 24 onwards is likely to have an impact on the serum tocilizumab concentration for the MSB11456 vs EU-RoActemra vs EU-RoActemra/MSB1146 treatment groups. However, as the SD for the three arms is wide and overlapping, it is not likely to be clinically relevant.

Special populations and interaction studies

No patients over the age of 55 were included in the PK studies, which is acceptable.

No clinical studies in special populations or interaction studies were submitted, which is acceptable for a biosimilar.

In the SmPC for MSB11456, the information in Section 4.5 "Interaction with other medicinal products and other forms of interaction" and Section "5.2 Pharmacokinetic properties" is the same as in the EU-RoActemra SmPC; and this is acceptable.

Pharmacodynamics

No validated PD marker exists that would be predictive of efficacy of tocilizumab in patients. However, the analysis of PD marker(s) as secondary endpoints in the clinical studies is considered supportive of similarity. In that regard, CRP, total IL-6, soluble IL-6 receptor, lipids (cholesterol and low-density lipoprotein (LDL) cholesterol) and absolute neutrophil count are relevant PD markers.

The pharmacodynamic comparability in terms of sIL-6R and CRP has been demonstrated in PK/PD study MS200740-001 between MSB11456 and reference product EU-RoActemra.

2.6.4. Conclusions on clinical pharmacology

The pivotal data for demonstrating PK similarity with the reference medicinal product are obtained from two single-dose studies in healthy volunteers: Study MS200740-0001 (single-dose 162 mg SC injection) and Study FKS456-002 (single-dose 8 mg/kg IV infusion). The available single-dose PK/PD data support biosimilarity of MSB11456 versus the EU-reference product RoActemra.

ADAs have an impact on the PK of tocilizumab but the response was similar for MSB11456 and EU-RoActemra.

The information in Section 4.5 "Interaction with other medicinal products and other forms of interaction" and Section "5.2 Pharmacokinetic properties" of the SmPC for Tyenne is the same as in the EU-RoActemra SmPC;

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

Study FKS456-001 does not contain any dose response data. The clinical trial included however, according to the applicant, some PK assessments. Steady state PK of MSB11456 and EU-RoActemra were compared by evaluating serum through concentrations (Ctrough) of tocilizumab over time in all patients.

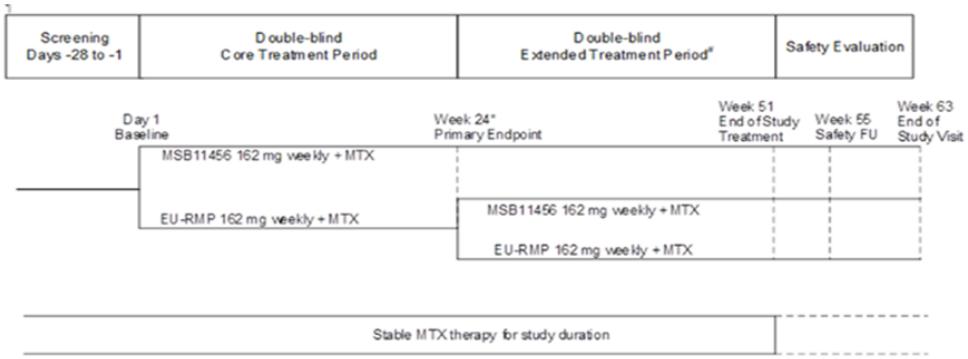
2.6.5.2. Main study(ies)

Title of study: A Randomized, Double-blind, Multiple-dose, Parallel-group, Two-arm Study to Evaluate the Efficacy, Safety, and Immunogenicity of MSB11456 Compared to European Union–approved RoActemra® in Patients with Moderately to Severely Active Rheumatoid Arthritis (APTURA I Study)

Methods

The pivotal study FKS456-001 was 1:1 randomised, double-blind, two arm study to evaluate the efficacy, safety and immunogenicity of MSB11456 compared to EU-RoActemra in patients with moderately to severely active RA (APTURA I study). The study included 604 patients with RA, 302 patients in each arm that were randomised to either MSB11456 or EU-RoActemra in prefilled syringe with a weekly injection of 162 mg subcutaneously (SC). Study FKS456-001 consists of a Screening period, a double-blind 24-week Core Treatment Period followed by an additional 28-week double-blind Extended Treatment Period and a 12-week Safety Evaluation Period. The schematic trial design is presented in Figure 6.

Figure 6 Study FKS456-001 Schematic



Source: CSR FKS456-001 Week 30, Figure 1

* At Week 24 visit, patients who were originally randomized to MSB11456 continued this treatment. Patients who were originally randomized to EU-RoActemra, were re-randomized in a 1:1 ratio to continue their weekly treatment with EU-RoActemra or to switch to MSB11456.

The 12-week Safety Evaluation starts at Week 51 and the Extended Treatment Period ends at Week 52.

EU-RMP = EU-RoActemra; FU = follow-up; MTX = methotrexate

Study Participants

Main inclusion criteria

The study population consisted of male or female patients aged ≥18 years old with moderately to severely active RA and inadequate response to therapy with at least one disease modifying anti-rheumatic drug (DMARD, either synthetic or biologic) and who were receiving a stable dose of methotrexate. The diagnosis of RA had to be made according to the revised 1987 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification 2010 criteria. Disease duration had to be ≥6 months prior to the Screening Visit. Moderately to severely active RA was defined by Swollen Joint Count ≥6 (66 joint count) and Tender Joint Count ≥6 (68 joint count) at screening and randomisation, radiographic evidence of ≥1 joint with a definite erosion attributable to RA at screening and C-reactive protein ≥1 mg/dL (≥10 mg/L) and/or erythrocyte sedimentation rate ≥28 mm/hour at screening. Previous use of any interleukin-6 (IL-6) acting drugs, targeted synthetic DMARDs like janus kinase inhibitors, any biological agent for a condition other than RA and more than two biologic treatments for RA were not allowed.

Exclusion criteria

Patients with rheumatoid arthritis classified as ACR functional class IV were excluded, as were patients with rheumatic autoimmune disease or inflammatory joint disease other than rheumatoid arthritis. Patients who had prior use of targeted synthetic DMARDs, more than 2 biologic treatments for rheumatoid arthritis, or any biological agent for a condition other than rheumatoid arthritis were also excluded.

The study enrolled patients from 81 investigative sites in Europe (Bulgaria, Czech Republic, Georgia, Hungary, Moldova, Poland, Russia, Serbia, and Slovakia). The study enrolment went from 03 Aug 2020-11 Oct 2021.

Treatments

Patients were assigned to the study drug in accordance with the randomisation schedule and received either MSB11456 or EU-RoActemra at a dose of 162 mg by SC injection starting at Day 1, then weekly up to Week 51. Randomisation was stratified by previous exposure to biologic treatment for RA. Patients who discontinued treatment early or violated the protocol were asked to continue to be followed for all regularly scheduled visits for safety and efficacy assessments up to the end of the corresponding treatment period. If a patient discontinued study drug prior to Week 24, the patient remained in the study up to the completion of the Week 24 assessments to allow for the collection of efficacy, safety and immunogenicity data for the assessment of similarity for a full 24-week period before switching occurs. Visits at site were on Weeks 1, 2, 4, 8, 12, 16, 24, 30, 42 and 52. The first 3 doses of MSB11456 (162 mg at Day 1, Day 8, and Day 15) were administered on site to ensure that the patient, or their caregiver was appropriately trained. The subsequent 2 doses (on Day 22 and Day 29) were also administered on site in the Czech Republic as per a request from the Czech Regulatory Authority. Patients were monitored for 2 hours following onsite administration. If, after proper training, the healthcare professional judged it appropriate, the patient (or a trained caregiver) could inject the following weekly doses of the MSB11456/ EU-RoActmera at home.

Objectives

<u>The primary objective was:</u>

to demonstrate equivalent efficacy of the proposed biosimilar tocilizumab MSB11456 and EU-RoActemra both administered SC to patients with moderately to severely active RA.

<u>The secondary objective was:</u>

to compare the safety, immunogenicity, and long-term efficacy of MSB11456 and EU-RoActemra.

The explanatory objectives were:

1) to explore the effect of a single treatment transition (i.e., in patients, who transitioned from EU-RoActemra to MSB11456 at Week 24) on efficacy, safety and immunogenicity and

2) to describe PK parameters of MSB11456 and EU-RoActemra.

Outcomes/endpoints

The study endpoints as pre-specified in the study protocol are summarised in Table 16.

Additionally, the applicant states that, based on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) addendum on estimands and sensitivity analysis in clinical trials and to the guideline on statistical principles for clinical trials (ICH, 2019), the study objective and endpoints described in the study protocol have been translated into key clinical questions of interest by means of the estimands framework in the statistical analysis plan (SAP) as agreed with both FDA and EMA prior to partial database lock and unblinding for the Week 30 analyses, see Statistical Methods section.

Table 16 Study endpoints of study FKS456-001

Primary Endpoints	Secondary Endpoints	Other and Exploratory Endpoints
Efficacy Endpoints		
DAS28-ESR mean absolute change from baseline at Week 24	DAS28-ESR mean absolute change from baseline at all assessment visits (except Week 1) (i.e., at Weeks 2, 4, 8, 12, 16, 30, 42 and 52) other than Week 24.	DAS28-CRP mean change from baseline at all assessment visits (except Week 1) (i.e., at Weeks 2, 4, 8, 12, 16, 24, 30, 42 and 52).
	ACR20 (20% improvement in ACR Core Set Measurements) response rate at Week 24.	ACR20 response rates at all assessment visits (except Week 1) other than Week 24.
		ACR50/70 (50% and 70% improvement in ACR Core Set Measurements) response rates at all assessment visits (except Week 1).
		Proportion of patients with DAS28-ESR and DAS28-CRP categorical responses (remission, Low Disease Activity and ACR/European League Against Rheumatism criteria (Boolean based) responses categories) at all assessment visits (except Week 1).
		Clinical Disease Activity Index and Simplified Disease Activity Index changes from baseline and categories (i.e., remission and Low Disease Activity) at all assessment visits (except Week 1).
Safety Endpoints		
	Occurrence of TEAE and SAE events up to Week 24, Week 30, Week 55 and Week 63.	Changes in vital signs, clinical laboratory values (hematology, clinical chemistry, urinalysis), abnormalities in 12-lead ECG and physical examination up to Week 24, Week 30, Week 55 and Week 63.
Immunogenicity Endpoints		
	ADA and NAb incidence, as well as ADA titers at Weeks 2, 12, 24, 30, 52 and 55.	
PK Endpoints		
		Trough concentration
		Model-based PK parameters (including, but not limited to, predicted C_{max} and AUC) using a population PK model*.

ADA = antidrug antibody; ACR = American College of Rheumatology; AUC = area under the concentration-time curve; C_{max} = maximum plasma concentration; DAS28-CRP = Disease Activity Score-28 C-Reactive Protein; DAS28-ESR = Disease Activity Score-28 Erythrocyte Sedimentation Rate; ECG = electrocardiogram; NAb = neutralizing antibody; PK = pharmacokinetics, SAE = serious adverse event, TEAE = treatment emergent adverse event.
*The exploratory model-based population PK parameters have not been generated as the number of patients was insufficient to perform the analysis and develop a meaningful solid population PK model.

Sample size

A sample size of 542 randomised patients (271 patients per arm) was chosen to provide approximately 460 patients (230 per arm) in the PP Analysis Set at Week 24, assuming a 15% drop-out rate (including major protocol deviations). The applicants states that this was based on the EMA recommendation a total of 460 evaluable patients (230 per arm) that would provide 90% power to demonstrate equivalence between treatments for the primary endpoint, with equivalence margins of ±0.6 and a Type I error of 2.5%, assuming no difference between the 2 treatment groups and a common standard deviation of 1.76.

In addition, this sample size would provide more than 80% power to demonstrate that the 95% CI for the difference between treatments in the key secondary endpoint (ACR20 response rate at Week 24) would be included in the equivalence interval [-15%, +15%], assuming no difference between the 2

treatment groups and that both MSB11456 and EU-RoActemra have an ACR20 response rate of 60% at Week 24. The actual number of patients finally enrolled was 604 (302 in ach treatment arm) marginally superseding the 10% over-enrolment.

Randomisation and Blinding (masking)

Patients with RA whose eligibility was confirmed at baseline were randomised 1:1 in a blinded fashion through an Interactive Response Technology (IRT) system to receive either MSB11456 or the EU-RoActemra. Randomisation was stratified by previous exposure to biologic treatment for rheumatoid arthritis. Patients who previously received 1 or 2 biologic treatments for rheumatoid arthritis were capped at 10% of the total study population. According to the applicant randomisation data were kept strictly confidential, accessible only to authorised staff, until the time of unblinding.

Participants and personnel involved in the conduct and the interpretation of the study were blinded to the participants' randomised treatment assignment during the study. Likewise, the double-blind nature of this study was maintained because at Week 24, after all efficacy and safety assessments were performed, all patients remaining on the investigational medical product (IMP) were re-randomised, including those in the MSB11456 group whose re-randomisation to continue the same treatment. Each IMP (MSB11456 and EU-RoActemra) syringe was blinded. Blinded labelled treatment kits were provided to each study site.

Statistical methods

The applicant states that the statistical analysis plan (SAP) detailing the statistical analyses were finalised prior to the Week 30 partial database lock.

The primary efficacy analysis at Week 24 was conducted after all patients had completed the Week 30 assessments or had withdrawn from the study before Week 30.

Analysis populations

Safety and immunogenicity data were listed and summarised using appropriate descriptive statistics on the Safety Analysis Set (SAF) and Extended Period Safety (EP-Safety) Analysis Set. Descriptive statistics were provided for results of the PK exploratory analyses (i.e., trough concentrations). The study analysis sets of FKS456-001 are presented in Table 17.

Table 17 Study analysis sets of FKS456-001

Analysis Set	Description
Intent-To-Treat (ITT)	The ITT Analysis Set includes all randomized patients. In the Extended Treatment Period, the EP-ITT Analysis Set includes all patients who entered into the Extended Treatment Period. Patients were analyzed according to their randomized treatment; for patients initially randomized to EU-RoActemra, this included both their initial and re-randomization assignment. The ITT Analysis Set was the primary analysis set for efficacy and was used for all primary, secondary and other efficacy endpoint analyses.
Per Protocol (PP)	The PP Analysis Set includes all randomized and treated patients (subgroup of the ITT Analysis Set) who completed the Core Treatment Period, attended the Week 24 visit with no clinically important protocol deviations before the primary efficacy endpoint analysis time point (Week 24), and who had a treatment compliance of ≥80% (including methotrexate compliance) in the Core Period. The Week 12 PP Analysis set includes all randomized and treated patients who attended the Week 12 visit with no clinically important protocol deviations before the Week 12 visit and who had a treatment compliance of ≥80% (including methotrexate compliance) up to the Week 12 visit. Patients were analyzed according to their randomized and received treatment, as receipt of a different treatment from that assigned is a major protocol deviation. The PP Analysis Set was used for the primary, secondary and other endpoint analyses.
Safety (SAF)	The Safety Analysis Set (SAF) included all patients who received at least one dose of study drug. In the Extended Treatment Period, the EP-SAF Analysis Set includes all patients who received at least 1 dose of study drug during the course of the Extended Treatment Period. Patients were analyzed according to the actual treatment they received. The SAF was used for all secondary and other safety, and immunogenicity endpoints analyses.
Pharmacokinetic (PK)	All patients who have at least one measurement of trough concentration and without important protocol deviations impacting PK. Patients were analyzed according to the actual treatment they receive.

Source: refer to SAP FKS456-001, Section 9.2
EP = Extended Treatment Period; ITT = intent to treat; PK = pharmacokinetics; PP = per-protocol; SAF = safety

Intercurrent events (ICE)

The primary, key secondary, and early efficacy (Week 12) estimands were defined in the Statistical Analysis Plan (SAP) with all of its attributes.

The following intercurrent events were defined:

•Treatment discontinuation or interruption due to AEs in patients with an IMP compliance of <80%;

•IMP discontinuation due to lack of efficacy;

•IMP discontinuation due to any other reason;

•Prohibited medications;

•Dose modification of methotrexate;

•COVID-19 vaccination;

Estimand and analyses

Primary Estimand 1.0 (DAS28-ESR Intent-to-Treat [ITT]) targeted the effect of study drug on the variable measurement regardless of adherence to the study drug or to the protocol, including use of prohibited medication prior to Week 24 and followed a 'treatment policy' strategy for all intercurrent events. Missing DAS28-ESR scores at Week 24 were imputed by a multiple imputation procedure under a MAR assumption. Nonmonotone missing data were imputed first, then the monotone missing values for each treatment group were imputed via the chained equation method. First, all missing data for the first post-baseline visit were imputed; then missing data for the next visit were imputed using observed data plus the just imputed missing data; and so on to the Week 24 visit. Baseline DAS28-ESR score and the randomisation stratification variable were used to model the distribution of trajectory values. Imputed DAS28-ESR scores were restricted such that the values were greater than zero.

The change from baseline at Week 24 in DAS28-ESR was analysed using an analysis of covariance with treatment group and previous exposure to biologic treatment for rheumatoid arthritis [yes/no] as fixed effects and baseline DAS28-ESR as a covariate. The stratification variable was used as entered in IRT. The difference between treatments was estimated by the least squares (LS) mean difference between MSB11456 and EU-RoActemra, with its 95% confidence interval (CI). The CI was compared with the equivalence interval of [-0.6, 0.6].

Supportive Estimand 1.1 (DAS28-ESR Per Protocol [PP]) targeted the effect of study drug on the variable measurement in the target population of those patients who adhered to the protocol and did not experience any clinically important protocol deviations impacting the primary endpoint.No imputation of missing data was performed.The same ANCOVA analysis as used for the primary estimand was performed on the PP Analysis Set. All data available were included in the analysis.

Supportive Estimand 1.2 (DAS28-ESR hypothetical return-to-baseline ITT) targeted the effect of study drug on the variable measurement in the target population as if the patient who discontinued or interrupted study drug due to study-related events (lack of efficacy or AE in patients with a study drug compliance of <80%) or took prohibited medication or had any methotrexate dose modification would no longer benefit from study drug. Measurements were projected as a worst case scenario, as if the patient's DAS28-ESR value returned to baseline levels immediately after the time of the intercurrent event ('hypothetical' strategy). For other intercurrent events, a treatment policy strategy was followed.

Imputation of missing DAS28-ESR values at Week 24 and imputation of discounted values due to the occurrence of relevant intercurrent events were based on a pattern-mixture model combining a baseline observation carried forward multiple imputation approach with missing at random (MAR) sequential imputation. For other missing data, MAR sequential imputation was used (as for the primary estimand). A similar analysis as for the primary estimand was performed with the exception that measurements that occurred after selected intercurrent events were not considered in the analysis.

Supportive Estimand 1.3 (DAS28-ESR hypothetical continuing per protocol ITT) targeted the effect of study drug on the variable measurement in the target population as if the patient who discontinued study drug for any reason or took prohibited medication or had any methotrexate dose modification, continued to follow the protocol after the time of the intercurrent event. Thus, for these intercurrent events, a 'hypothetical' strategy was followed where measurements were projected as a per protocol scenario. For the other intercurrent events, a treatment policy was followed.

A similar analysis as for the primary estimand was performed, with the exception that the following DAS28-ESR assessments were discounted and those now missing visits were imputed using multiple imputation as in the primary analysis: DAS28-ESR values that occurred after treatment discontinuation

due to any reason and DAS28-ESR values that occurred after use of prohibited medication (or modification of permitted medications) that could impact Week 24 efficacy.

*The following **sensitivity analyses** on the primary estimand were performed on the ITT population:*

- *no imputation of missing values.*
- *a tipping point analysis, based on the same analysis of covariance model as for the primary analysis.*

The **Key Secondary Estimand 2.0** (ACR20 ITT) targeted the effect of study drug on the variable measurement regardless of adherence to the study drug or to the protocol, including use of prohibited medication prior to Week 24 and followed a 'treatment policy' strategy for all intercurrent events. Missing ACR20 response data were imputed using the last observation carried forward (LOCF) method. All missing ACR20 assessments were imputed using the last non-missing assessment. Patients who had just a baseline assessment had their postbaseline assessments imputed as non-responders. LOCF was proposed because few missing ACR assessments were expected at Week 24. However, a sensitivity analysis using multiple imputation was proposed to address any situation in which there was a large number of missing values at Week 24.

The difference in ACR20 response rate at Week 24 was compared using a 95% stratified Newcombe CI to adjust for the stratification factor previous exposure to biologic treatment for rheumatoid arthritis [yes/no] and assessed against an equivalence margin of [-15%, 15%]. Mantel-Haenszel weights were used to combine the stratum components.

Supportive Estimand 2.1 (ACR20 PP) targeted the effect of study drug on the variable measurement in the target population of those patients who adhered to the protocol and did not experience any clinically important protocol deviations. The same analysis method as the key secondary estimand was performed on the PP Analysis Set. No patients in the PP Analysis Set had missing ACR20 data at Week 24.

Supportive Estimand 2.2 (ACR20 hypothetical non-responder ITT) targeted the effect of study drug on the variable measurement in the target population as if the patient who discontinued or interrupted study drug due to study-related events (lack of efficacy or AE in patients with a study drug compliance of <80%) or took prohibited medication or had any methotrexate dose modification would no longer benefit from study drug. Measurements were projected as a worst case scenario, as if the patient's ACR20 was considered as a nonresponse immediately after the time of the intercurrent event ('hypothetical' strategy). For other intercurrent events, a treatment policy strategy was followed.

A similar analysis as for the Key Secondary Estimand 2.0 was carried out with the exception that measurements that occurred after selected intercurrent events were not considered in the analysis. Imputation of missing ACR20 response data at Week 24 and imputation of discounted values due to the occurrence of relevant intercurrent events was based on a combination of a non-responders approach with LOCF. The non-responders approach was used for patients who discontinued from IMP prior to Week 24 due to lack of efficacy or due to an AE and/or for patients who used prohibit*ed* medication or modified their permitted medications prior to Week 24. For other missing data, LOCF was used (as for the key secondary estimand).

The following **sensitivity analyses** on the Key Secondary Estimand were performed on the ITT population:

- No imputation.
- Missing ACR20 values were imputed using a multiple imputation approach.
- A tipping point analysis

Early (Week 12) efficacy estimands **Supportive Estimand 3.0, Supportive Estimand 3.1,** and **Supportive Estimand 3.2** were constructed based on DAS28-ESR at Week 12 with the same attributes as Primary Estimand 1.0, Supportive Estimand 1.1, and Supportive Estimand 1.3 respectively.

Type-I Error Control

There was no adjustment for multiplicity because this study had only one primary endpoint, and study success were evaluated according to the success criterion defined for each agency.

Analyses of Subgroups

Analyses on the primary and key secondary estimands (Estimand 1.0, and Estimand 2.0 as described above) were to be performed for the following subgroups using the same methods as the main analyses, removing the strata from the model, when applicable:

- Previous exposure to biologic treatment for RA [yes/no]
- ADA positive/ADA negative
- Neutralising antibody (NAb) positive/NAb negative
- Non COVID-19 vaccinated/COVID-19 vaccinated prior to Week 24
- Non COVID-19 vaccinated/COVID-19 vaccinated prior to Week 12 for Estimand 3.0 (DAS28 ESR at Week 12)

Of note: Previous exposure to biologic treatment for RA and COVID-19 vaccinated, subgroup analyses were to be performed only if at least 10% of the ITT or PP set in each subgroup. ADA or NAb status were defined as positive for a complete study period if the patient had at least 1 confirmatory positive result post-dose any time during this period. Otherwise, the status was defined as negative for this complete study period. A forest plots were to be displayed with the analysis by each of the subgroups as well as overall.

Secondary analyses

For secondary and other efficacy variables, mixed-effect repeated measure models were employed for the analysis of longitudinal continuous data. The fixed effects of treatment, visit, treatment-by-visit interaction, and stratification factor were included in the model and the 95% CI of the LS mean was provided for each time point.

Categorical variables were summarised descriptively. The Core Period tables utilised the ITT and PP Analysis Sets, and the Extended Period tables utilised the Extended Period Intent-to-Treat (EP-ITT Analysis Set).

Results

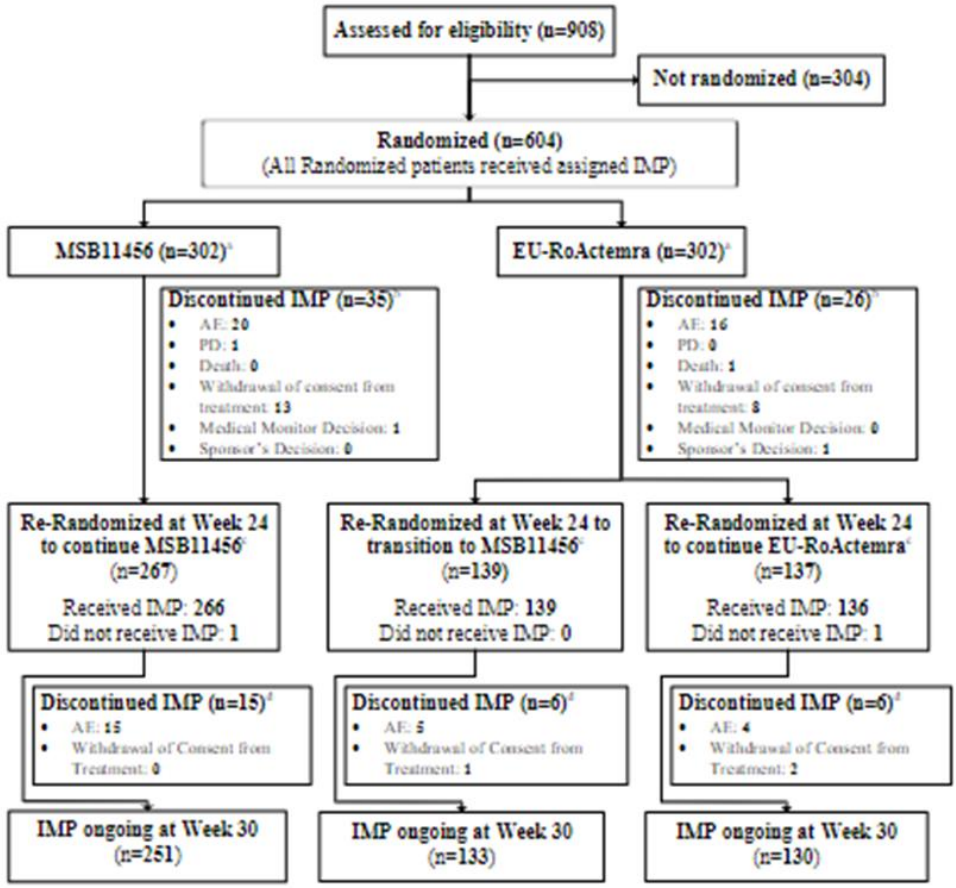
Participant flow

Subject disposition in Study FKS456-001 is summarised Figure 7. Of the 908 patients screened, a total of 604 patients were randomised to receive study drug administered SC according to the randomised treatment (302 per arm) and were included in the Safety Analysis Set. According to the applicant similar proportions of patients in the MSB11456 and EU-RoActemra groups discontinued study drug prior to Week 24 (35 [11.6%] and 26 [8.6%], respectively). The main reasons for discontinuing study drug prior to Week 24 in both groups included AE(s) and withdrawal of consent from treatment. Overall, similar proportions of patients in the MSB11456 and EU-RoActemra groups were rerandomised in the Extended Treatment Period (267/302 [88.4%] and 276/302 [91.4%] of patients, respectively), and most patients (541/543 [99.6%]) received study drug during the Extended Treatment Period.

The applicants further states that other than 1 patient who received 1 dose of EU-RoActemra instead of MSB11456 at Week 25, all patients received study drug according to the re-randomised treatment and were included in the EP-SAF Analysis Set: 266 patients who continued MSB11456; 139 patients who transitioned from EU-RoActemra to MSB11456, and 136 patients who continued EU-RoActemra. Hereafter, these treatment groups will be referred to as the MSB11456 group, the EU-RoActemra / MSB11456 group, and the EU-RoActemra group, respectively, in the context of the Overall or Extended Treatment Periods.

In the EP-SAF Analysis Set, study drug was ongoing at Week 30 in similar proportions of patients in each treatment group (approximately 95.0% of patients overall). The main reason for discontinuing study drug during the Extended Treatment Period prior to Week 30 was AE(s) in all treatment groups.

Figure 7 Subject disposition in Study FKS456-001



Source: CSR FKS456-001, Figure 2

AE = adverse event, EU-RoActemra = European Union–approved RoActemra, IMP = investigational medicinal product, PD = protocol deviation

Note: A patient could have more than 1 reason for discontinuation.

[a] Core Period: MSB11456 and RMP groups.

[b] Patients discontinued IMP within the Core Period. Patients who completed Core Period IMP could have ongoing treatment at Week 24.

[c] Extended Period and Overall Period: MSB11456, RMP-to-MSB11456, and RMP groups.

[d] Patients discontinued IMP within the Extended Period after re-randomization.

Protocol Deviations

A major protocol deviation was defined as a deviation that had a major impact on data quality or patient safety or led to death. A clinically important protocol deviation was defined as a major

deviation likely to affect the efficacy of treatment. The major protocol deviations are presented in Table 18.

Table 18 Major protocol deviations-Core treatment period (ITT)

Deviation Category/ Deviation [n (%)]	MSB11456 (N=302)	EU-RoActemra (N=302)	Total (N=604)
Week 24			
Major Protocol Deviations	141 (46.7)	130 (43.0)	271 (44.9)
LABORATORY ASSESSMENT	59 (19.5)	66 (21.9)	125 (20.7)
VISIT SCHEDULE	50 (16.6)	31 (10.3)	81 (13.4)
CONCOMITANT MEDICATION	35 (11.6)	28 (9.3)	63 (10.4)
SAEs /AESI	14 (4.6)	19 (6.3)	33 (5.5)
STUDY PROCEDURES	13 (4.3)	16 (5.3)	29 (4.8)
INFORMED CONSENT	9 (3.0)	6 (2.0)	15 (2.5)
IMP COMPLIANCE	5 (1.7)	5 (1.7)	10 (1.7)
ELIGIBILITY & ENTRY	3 (1.0)	2 (0.7)	5 (0.8)
ADMINISTRATIVE	5 (1.7)	1 (0.3)	6 (1.0)
VISIT SCHEDULE CRITERIA	3 (1.0)	0	3 (0.5)
Major Protocol Deviations Leading to Exclusion from Week 24 PP Analysis Set (Clinically Important)	5 (1.7)	4 (1.3)	9 (1.5)
VISIT SCHEDULE	4 (1.3)	3 (1.0)	7 (1.2)
ELIGIBILITY & ENTRY	1 (0.3)	1 (0.3)	2 (0.3)
Major Protocol Deviations Leading to Exclusion from Week 24 PK Analysis Set	0	1 (0.3)	1 (0.2)
ELIGIBILITY & ENTRY	0	1 (0.3)	1 (0.2)

Source: refer to CSR FKS456-001, Table 14.1.2.1.1

AESI = adverse event of special interest, EU RoActemra = European Union–approved RoActemra, IMP = investigational medicinal product, ITT = Intent to Treat, PK = pharmacokinetics, PPS = Per Protocol Analysis Set, SAE = serious adverse event

Note: For each deviation, patients were included only once, even if they experienced multiple events within a deviation.

Recruitment

The study period for enrolment went from 03 Aug 2020- 11 Oct 2021. The study enrolled patients from 81 investigative sites in Europe (Bulgaria, the Czech Republic, Georgia, Hungary, Moldova, Poland, Russia, Serbia, and Slovakia).

Conduct of the study

Up to the time of unblinding for this Week 30 CSR, there were 2 global amendments of the original protocol. In addition, local amendments were implemented. The two substantial global amendments are summarised below:

Protocol Version 2.0 (Global Amendment 1; substantial), dated 06 May 2020:

-Measures implemented to increase safeguarding for the patients due to COVID19 pandemic

▪ Implementation of risk minimisation and the mitigation plan for COVID-19.

▪ Provision of a separate ICF to inform patients of the nature and impact of COVID-19.

▪ Updates to the exclusion criteria to exclude patients with confirmed or suspected active COVID-19 infection and to ensure that the investigator specifically evaluates the patient's eligibility taking into consideration COVID-19 risk factors and situation.

▪ Provided details of action to take with the IMP due to COVID-19 and confirmed details of COVID-19 AE/SAE reporting.
▪ Permitted the inclusion of local laboratories (with preapproval of the Sponsor) instead of central laboratories, if required due to the COVID-19 situation.

-Further details of injection site reactions and reporting, and instructions for the investigator to t if such reaction had occurred since the last assessment.

- Replaced predefined AESIs with a statement that any AEs that lead to interruption of IMP, permanent discontinuation of IMP, or withdrawal from the study will be considered predefined AESIs

Protocol Version 3.0 (Global Amendment 2; substantial), dated 01 Feb 2021:
-Added that COVID-19 vaccination was not allowed from 4 weeks prior to randomisation until the completion of the Week 30 visit (COVID-19–related protocol deviation)
-Removed details regarding North America, Asia, and the Rest of the World, including stratification by geographical region, as the study was being conducted in Europe only.

Baseline data

Baseline demographic and disease characteristics of the trial population (ITT population) are summarised in Table 19 and Table 20 respectively. The applicant states that baseline demographics and baseline disease characteristics were similar for the PP Analysis Set compared to the ITT Analysis Set.

Table 19 Baseline Demographics (study FKS456-001, ITT analysis set)

Characteristic	MSB11456 (N=302)	EU-RoActemra (N=302)	Total (N=604)
Sex [n (%)]			
Female	250 (82.8)	248 (82.1)	498 (82.5)
Male	52 (17.2)	54 (17.9)	106 (17.5)
Race [n (%)]			
White	302 (100)	302 (100)	604 (100)
Black or African American	0	0	0
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	0	0	0
Not Reported	0	0	0
Ethnicity [n (%)]			
Hispanic or Latino	1 (0.3)	2 (0.7)	3 (0.5)
Not Hispanic or Latino	300 (99.3)	300 (99.3)	600 (99.3)
Not Reported	1 (0.3)	0	1 (0.2)
Age (years)			
n (missing)	302 (0)	302 (0)	604 (0)
Mean (SD)	51.2 (12.72)	53.2 (11.33)	52.2 (12.08)
Median	52.0	54.0	53.0
Min, Max	19, 79	21, 78	19, 79
Baseline Weight (kg)			
n (missing)	302 (0)	302 (0)	604 (0)
Mean (SD)	73.63 (14.110)	71.76 (13.518)	72.70 (13.837)
Median	72.40	70.60	71.75
Min, Max	40.0, 99.5	43.0, 118.0	40.0, 118.0
Height (cm)			
n (missing)	302 (0)	302 (0)	604 (0)
Mean (SD)	165.36 (8.104)	165.42 (8.138)	165.39 (8.114)
Median	165.00	165.00	165.00
Min, Max	144.5, 189.0	145.0, 190.0	144.5, 190.0
Baseline BMI (kg/m^2)*			
n (missing)	302 (0)	302 (0)	604 (0)
Mean (SD)	26.91 (4.740)	26.22 (4.597)	26.56 (4.677)
Median	26.72	26.03	26.31
Min, Max	16.4, 40.7	16.3, 43.5	16.3, 43.5

Source: refer to CSR FKS456-001 Week 30, Table 14.1.3.1.1
BMI = Body Mass Index; ITT = Intent-to-Treat; SD = standard deviation
Unless otherwise noted, demographic characteristics were assessed at Screening.

Table 20 Endpoint Baseline disease characteristics (Study FKS456-001, ITT analysis set)

Characteristic	MSB11456 (N=302)	EU-RoActemra (N=302)	Total (N=604)
DAS28-ESR			
n (missing)	302 (0)	302 (0)	604 (0)
Mean (SD)	6.28 (0.787)	6.26 (0.795)	6.27 (0.791)
Median	6.2	6.2	6.2
Min, Max	3.0, 8.3	3.3, 8.1	3.0, 8.3
Remission	0	0	0
Low	1 (0.3)	0	1 (0.2)
Moderate	16 (5.3)	22 (7.3)	38 (6.3)
High	285 (94.4)	280 (92.7)	565 (93.5)
Missing	0	0	0
DAS28-CRP			
n (missing)	302 (0)	302 (0)	604 (0)
Mean (SD)	5.44 (0.896)	5.42 (0.869)	5.43 (0.882)
Median	5.4	5.3	5.4
Min, Max	2.5, 8.0	2.9, 7.6	2.5, 8.0
Clinical Disease Activity Index (CDAI)			
Remission	0	0	0
Low	1 (0.3)	1 (0.3)	2 (0.3)
Moderate	16 (5.3)	21 (7.0)	37 (6.1)
High	285 (94.4)	280 (92.7)	565 (93.5)
Missing	0	0	0
Simplified Disease Activity Index (SDAI)			
Remission	0	0	0
Low	1 (0.3)	1 (0.3)	2 (0.3)
Moderate	33 (10.9)	36 (11.9)	69 (11.4)
High	268 (88.7)	265 (87.7)	533 (88.2)
Missing	0	0	0
ADA			
n (missing)	302 (0)	302 (0)	604 (0)
Positive [n (%)]	20 (6.6)	25 (8.3)	45 (7.5)
Negative [n (%)]	282 (93.4)	277 (91.7)	559 (92.5)
ADA Titer			
n (missing)	20 (0)	25 (0)	45 (0)
Mean (SD)	108.00 (200.987)	252.00 (407.676)	188.00 (336.652)
Median	60.0	60.0	60.0
Min, Max	60.0, 960.0	60.0, 1920.0	60.0, 1920.0
NAb			
n (missing)	302 (0)	302 (0)	604 (0)
Positive [n (%)]	0	0	0
Negative [n (%)]	20 (6.6)	25 (8.3)	45 (7.5)
Not tested [n (%)]	282 (93.4)	277 (91.7)	559 (92.5)

Source: refer to CSR FKS456-001 Week 30, Table 14.1.3.2.1
ADA = antidrug antibody; CDAI = Clinical Disease Activity Index; DAS28-CRP = Disease Activity Score-28 C-Reactive Protein; DAS28-ESR = Disease Activity Score-28 Erythrocyte Sedimentation Rate; ITT = intent to treat; NAb = neutralizing antibody; SDAI = Simplified Disease Activity Index; SD = standard deviation
DAS28-ESR: Remission = DAS28-ESR <2.6; Low = 2.6 ≤ DSA28-ESR <3.2; Moderate = 3.2 ≤ DAS28-ESR ≤5.1; High = 5.1 < DAS28-ESR
CDAI: Remission = CDAI ≤2.8; Low = 2.8 < CDAI ≤10; Moderate = 10 < CDAI ≤22; High = 22 < CDAI
SDAI: Remission = SDAI ≤3.3; Low = 3.3 < SDAI ≤11; Moderate = 11 < SDAI ≤26; High = 26 < SDAI
Note: For ADA titer summaries, values below the lower limit of quantification were imputed using the lower limit of quantification.

Medical History of Rheumatoid arthritis and Concurrent Illnesses

The medical history of the patients' rheumatoid arthritis disease and concurrent illnesses is depicted in Table 21. According to the applicant, and in line with the eligibility criteria, all patients in the ITT

Analysis Set had been diagnosed with rheumatoid arthritis ≥6 months prior to the Screening visit and were ACR functional Class I to Class III.

Overall, similar proportions of patients in the MSB11456 and EU-RoActemra groups (9.3% and 8.6% respectively) had previous exposure to any biologic treatment for rheumatoid arthritis. Likewise, the applicant states that a similar proportion of patients in the MSB11456 and EU-RoActemra groups received COVID 19 vaccination prior to the Week 12 visit (5.6% and 6.6% respectively) and prior to the Week 24 visit (11.6% and 9.9% respectively).

Regarding extra-articular manifestations of rheumatoid arthritis, 17.7% of patients were known to have rheumatoid nodules, 4.5% secondary Sjogrens Syndrome, and 1.8% of patients were known to have peripheral neuropathy. The incidence of each of the other extra articular manifestations was ≤1.0%, Table 21.

Table 21 Rheumatoid arthritis history- Core period (ITT analysis set)

Characteristic	MSB11456 (N=302)	EU-RoActemra (N=302)	Total (N=604)
Functional Classification [n (%)]			
Class I	25 (8.3)	17 (5.6)	42 (7.0)
Class II	231 (76.5)	246 (81.5)	477 (79.0)
Class III	46 (15.2)	39 (12.9)	85 (14.1)
Class IV	0	0	0
Missing	0	0	0
Previous Use of Biologic Treatment [n (%)]			
Yes	28 (9.3)	26 (8.6)	54 (8.9)
No	274 (90.7)	276 (91.4)	550 (91.1)
Missing	0	0	0
Time since symptom onset (months)			
n (missing)	299 (3)	299 (3)	598 (6)
Mean (std)	110.55 (88.191)	110.47 (88.478)	110.51 (88.261)
Median	86.0	85.0	85.5
Min, Max	8.0, 476.0	9.0, 441.0	8.0, 476.0
Time since first RA diagnosis (months)			
n (missing)	300 (2)	300 (2)	600 (4)
Mean (std)	95.24 (79.912)	90.90 (83.466)	93.07 (81.669)
Median	73.0	65.5	69.0
Min, Max	7.0, 372.0	7.0, 441.0	7.0, 441.0
Time from first symptoms to diagnosis (months)			
n (missing)	299 (3)	299 (3)	598 (6)
Mean (std)	15.32 (32.596)	19.61 (35.494)	17.46 (34.115)
Median	5.0	7.0	6.0
Min, Max	-5.0, 372.0	0.0, 246.0	-5.0, 372.0
Extra-Articular Manifestations [n (%)]			
Rheumatoid Nodules			
Yes	44 (14.6)	63 (20.9)	107 (17.7)
No	256 (84.8)	239 (79.1)	495 (82.0)
Unknown	2 (0.7)	0	2 (0.3)
Missing	0	0	0
Vasculitis			
Yes	1 (0.3)	1 (0.3)	2 (0.3)
No	301 (99.7)	301 (99.7)	602 (99.7)
Unknown	0	0	0
Missing	0	0	0

Table 22 continued Rheumatoid arthritis history- Core period (ITT analysis set)

Characteristic	MSB11456 (N=302)	EU-RoActemra (N=302)	Total (N=604)
Interstitial Lung Disease			
Yes	1 (0.3)	2 (0.7)	3 (0.5)
No	301 (99.7)	300 (99.3)	601 (99.5)
Unknown	0	0	0
Missing	0	0	0
Pleuritis			
Yes	0	1 (0.3)	1 (0.2)
No	302 (100.0)	301 (99.7)	603 (99.8)
Unknown	0	0	0
Missing	0	0	0
Amyloidosis			
Yes	0	0	0
No	302 (100.0)	302 (100.0)	604 (100.0)
Unknown	0	0	0
Missing	0	0	0
Cryoglobulinaemia			
Yes	0	0	0
No	300 (99.3)	300 (99.3)	600 (99.3)
Unknown	2 (0.7)	2 (0.7)	4 (0.7)
Missing	0	0	0
Peripheral Neuropathy			
Yes	7 (2.3)	4 (1.3)	11 (1.8)
No	294 (97.4)	298 (98.7)	592 (98.0)
Unknown	1 (0.3)	0	1 (0.2)
Missing	0	0	0
Secondary Sjogren's Syndrome			
Yes	14 (4.6)	13 (4.3)	27 (4.5)
No	286 (94.7)	288 (95.4)	574 (95.0)
Unknown	2 (0.7)	1 (0.3)	3 (0.5)
Missing	0	0	0

EU-RoActemra = European Union-approved RoActemra, ITT = Intent-to-Treat, RA = rheumatoid arthritis
Source: Listing 16.2.4.5.1, 16.2.4.5.2, Dataset: ADMH, Program: t-rah-core-itt.sas, Output: T-14-01-04-01-01-rah-core-itt.rtf, Generated on: 09FEB2022 at 02:56

Prior medication

Prior medications defined as any medication discontinued prior to the first dose of study drug, had been taken by 76.5% of patients in the ITT Analysis Set. The most commonly reported prior medications were those taken for the rheumatoid arthritis disease under study. Prior medication taken by ≥ 5% of the patients in either treatment group is presented in Table 23.

The applicant further states that COVID-19 vaccines were reported as prior medications for 5 patients in the ITT Analysis Set, 4 (1.3%) patients in the MSB11456 group and 1 (0.3%) patient in the EU-RoActemra group. As already described prior biologic medications for the disease under study were taken by less than 10% of patients n=54) and included the selective immunosuppressant abatacept, and tumour necrosis factor inhibitors (adalimumab, infliximab, etanercept, golimumab, certolizumab pegol, certolizumab, and ABP501 (i.e. biosimilar amgevita).

Of note, to be eligible for the study, all patients had to have been treated with methotrexate for at least 12 consecutive weeks immediately prior to randomisation and were on a stable dose of between

10 and 25 mg/week methotrexate for the last 8 weeks prior to screening. The dose and route of administration of methotrexate at study entry was to be continued without change during the study, in particular during the 52-week treatment period of the study.

Table 23 Prior medication taken by ⩾ 5% of the patients in either treatment group (ITT analysis set)

Preferred Name in ≥5% patients [n (%)]	MSB11456 (N=302)	EU-RoActemra (N=302)	Total (N=604)
Any Prior Medications	230 (76.2)	232 (76.8)	462 (76.5)
METHOTREXATE	164 (54.3)	171 (56.6)	335 (55.5)
METHYLPREDNISOLONE	96 (31.8)	93 (30.8)	189 (31.3)
SULFASALAZINE	54 (17.9)	45 (14.9)	99 (16.4)
DICLOFENAC	34 (11.3)	37 (12.3)	71 (11.8)
HYDROXYCHLOROQUINE	43 (14.2)	25 (8.3)	68 (11.3)
LEFLUNOMIDE	29 (9.6)	30 (9.9)	59 (9.8)
CHLOROQUINE	22 (7.3)	22 (7.3)	44 (7.3)
FOLIC ACID	14 (4.6)	23 (7.6)	37 (6.1)
MELOXICAM	19 (6.3)	18 (6.0)	37 (6.1)

EU-RoActemra = European Union-approved RoActemra, ITT = Intent-to-Treat, WHO = World Health Organization
Note: Prior medications are defined as any medication discontinued prior to the first dose of investigational medicinal product and were coded using WHO Drug Dictionary Version 2020SEP01. Prior medications taken by ≥5% of patients in either treatment group are summarized.
Source: Table 14.1.5.1.1

Numbers analysed

The ITT Analysis Set (n=604) was used as the primary analysis set for efficacy and was used for all primary, secondary and other efficacy endpoint analyses.

The PP Analysis Set (n= 497) was used as a sensitivity analysis for the primary, secondary and other efficacy endpoint analysis.

The Safety Analysis Set (n=604) was used for all secondary and other safety, and immunogenicity endpoints analyses. Among the 604 patients included in the Safety Analysis Set for the Overall Period (Day 1 to Week 30), 541 patients were included in the Extension period -Safety Analysis Set for the Extended Period (Week 24 to Week 30).

Table 24 Patient analyses sets- Core period (all screened patients)

Analysis Set Reason for Exclusion	MSB11456	EU-RoActemra	Total
Pharmacokinetic Analysis Set[d] (PK) [n (%)]	302 (100)	301 (99.7)	603 (99.8)
Reasons for Exclusions from PK Set			
No Trough Concentration Measurement	0	0	0
Major Pharmacokinetic Protocol Deviation	0	1 (0.3)	1 (0.2)
COVID-19 Vaccination Subgroup [n (%)]			
Prior to Week 24 Visit	35 (11.6)	30 (9.9)	65 (10.8)
Prior to Week 12 Visit	17 (5.6)	20 (6.6)	37 (6.1)
Strata within IXRS [n (%)]			
Previous Exposure to Biological Treatment for RA	28 (9.3)	26 (8.6)	54 (8.9)
No Previous Exposure to Biological Treatment for RA	274 (90.7)	276 (91.4)	550 (91.1)

Note: Patients can have more than one reason for exclusion from the Analysis Set.
Percentages are based on all randomized patients with the exception of "Not Randomized" and "Trial screen failure" subjects which are based on the number of screened subjects.

a ITT Analysis Set includes all randomized patients and is analyzed according to the randomized treatment.
b Safety Analysis Set includes all randomized and treated patients and is analyzed according to the actual treatment received.
c PP Analysis Set includes all randomized and treated patients who do not have any clinically important major protocol deviations before week 24/week 12 respectively and is analyzed according to the randomized and received treatment on Day 1.
d Pharmacokinetic Analysis Set includes all patients with at least one trough concentration measurement and no major pharmacokinetic protocol deviations.

Outcomes and estimation

Primary endpoint and primary estimand 1.0

The primary endpoint, i.e., DAS28-ESR change from baseline at Week 24 (Primary Estimand 1.0) in the ITT Analysis Set is summarised in Table 25. The difference between treatment groups was estimated by the least squared (LS) mean difference between MSB11456 and EU-RoActemra, with its 95% CI for the EMA (equivalence interval of [-0.6, 0.6]) and its 90% CI for the FDA (equivalence interval of [-0.6, 0.5]). LS mean decreases in DAS28-ESR from baseline were present at Week 24 in both the MSB11456 and EU-RoActemra treatment groups for the ITT Analysis Set.

The results of the statistical analysis of the primary estimand showed no difference between MSB11456 and EU-RoActemra, with the 95% CIs for the differences in DAS28-ESR change from baseline at Week 24 between groups fully included within the respective predefined equivalence intervals, Table 25.

Table 25 Study FKS45611-001 Primary endpoint DAS28-ESR Change from Baseline at week 24 (ITT)

Variable Statistic	MSB11456 (N=302)	EU-RoActemra (N=302)	Difference MSB11456 – EU-RoActemra (N=604)
Change from Baseline to Week 24			
LS Mean (SE)[a]	-3.53 (0.105)	-3.54 (0.105)	
95% Confidence Interval[a]	(-3.74, -3.32)	(-3.75, -3.34)	
Number of Imputed Values	25	17	
Difference in Change from EU-RoActemra[a]			
LS Mean Difference (SE)			0.01 (0.104)
95% Confidence Interval[b]			(-0.19, 0.22)

Source: refer to CSR FKS456-001 Week 30, Table 14.2.1.1

ANCOVA = analysis of covariance, DAS28-ESR = Disease Activity Score-28 Erythrocyte Sedimentation Rate, EMA = European Medicines Agency, FDA = Food and Drug Administration, IMP = investigational medicinal product, IRT = interactive response technology, ITT = Intent-to-Treat, LS = least squares, SE = standard error

[a] LS means, standard errors, and confidence intervals are from an ANCOVA model based on change from baseline in DAS28-ESR with fixed effects for IMP and previous exposure to biologic treatment for rheumatoid arthritis [Y / N] and baseline DAS28-ESR as a covariate. Fixed effects were based on IRT.

[b] MSB11456 was considered equivalent to EU-RoActemra if the 95% confidence interval was included in the equivalence interval of [-0.6, 0.6].

Note: Primary endpoint: comparison made as per randomized treatment policy regardless of potential treatment discontinuation or background therapy change. Missing outcome values imputed by means of a multiple imputation approach assuming missing at random and using ANCOVA model covariates to model the distribution of trajectory values.

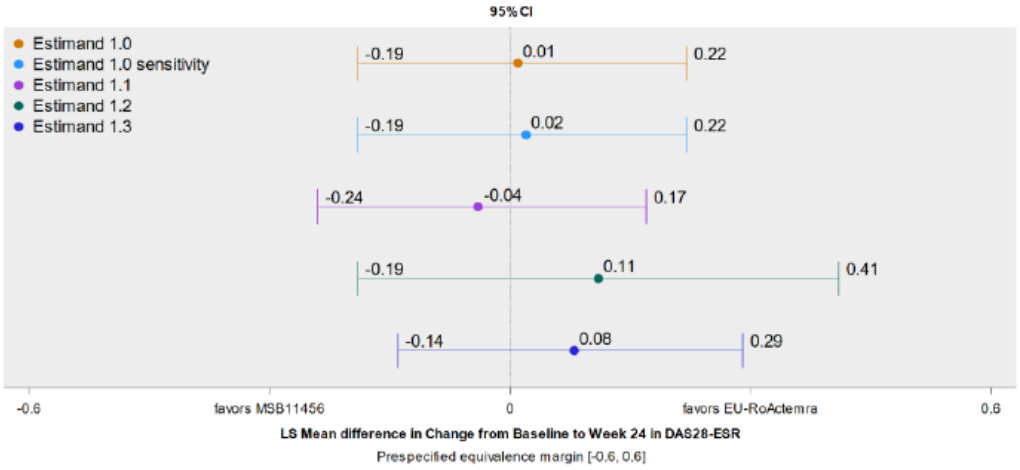
Supportive Estimand 1.1, 1.2 and 1.3

The statistical analysis of *Supportive Estimand 1.1* was conducted in the PP Analysis Set. The results of the statistical analysis of Supportive Estimand 1.1 were similar to those of Primary Estimand 1.0, i.e., and the 95% CIs for the differences in change from baseline between treatment groups fully included the respective predefined equivalence intervals.

DAS28-ESR change from baseline at Week 24 in the ITT Analysis Set *(Supportive Estimand 1.2)* is targeted the effect of study drug on the variable measurement in the target population as if the patient who discontinued or interrupted study drug due to study-related events (lack of efficacy or AE in patients with a study drug compliance of < 80%) or took prohibited medication or had any methotrexate dose modification would no longer benefit from study drug. The results of the statistical analysis of Supportive Estimand 1.2 showed no differences between MSB11456 and EU-RoActemra, with the 95% CIs for the differences in change from baseline between groups fully included within the respective predefined equivalence intervals. Likewise the analysis of DAS28-ESR change from baseline at Week 24 in the ITT Analysis Set *(Supportive Estimand 1.3)* showed no difference between MSB11456 and EU-RoActemra, with the 95% CIs for the differences in change from baseline between groups fully included within the respective predefined equivalence intervals.

An overview of all results of the statistical analyses of primary Estimands and supportive Estimands 1.1, 1.2 and 1.3 is presented in Figure 8 Estimands 1: 95% CI for the LS mean difference in change from baseline to week 24 in DAS28-ESR between MSB11456 and EU-Roactemra.

Figure 8 Estimands 1: 95% CI for the LS mean difference in change from baseline to week 24 in DAS28-ESR between MSB11456 and EU-Roactemra



Source: refer to CSR FKS456-001 Week 30, Table 14.2.1.1, Table 14.2.2.4, Table 14.2.2.1, Table 14.2.2.2 and Table 14.2.2.3

CI = confidence interval, DAS28-ESR = Disease Activity Score-28 Erythrocyte Sedimentation Rate, LS = least squares

Note: Estimand 1.0 sensitivity is the sensitivity analysis with no imputation.

LS means and confidence intervals (CI) are from an ANCOVA model based on change from baseline in DAS28-ESR with fixed effects for study drug and previous exposure to biologic treatment for RA [Y/N] and baseline DAS28-ESR as a covariate.

Sensitivity analyses

No Imputation

DAS28-ESR change from baseline at Week 24 with no imputation of data (i.e., discounted patients with a missing week 24 DAS28-ESR value) for the ITT Analysis Set is presented in Table 26.

Table 26 DAS28-ESR-Change from baseline at week 24- No imputation (ITT analysis set)

Variable Statistic	MSB11456 (N=302)	EU-RoActemra (N=302)	Difference MSB11456 – EU-RoActemra (N=604)
Change from Baseline to Week 24			
LS Mean (SE)[a]	-3.57 (0.107)	-3.59 (0.107)	
95% Confidence Interval[a]	(-3.78, -3.36)	(-3.80, -3.38)	
Number of Missing Values	25	17	
Difference in Change from EU-RoActemra[a]			
LS Mean Difference (SE)[b]			0.02 (0.105)
90% Confidence Interval[b]			(-0.16, 0.19)
95% Confidence Interval[b]			(-0.19, 0.22)

ANCOVA = analysis of covariance, DAS28-ESR = Disease Activity Score-28 Erythrocyte Sedimentation Rate, EMA = European Medicines Agency, EU-RoActemra = European Union–approved RoActemra, FDA = Food and Drug Administration, IMP = investigational medicinal product, IRT = interactive response technology, ITT = Intent-to-Treat, LS = least squares, SE = standard error

[a] LS means, standard errors, and confidence intervals are from an ANCOVA model based on change from baseline in DAS28-ESR with fixed effects for IMP and previous exposure to biologic treatment for rheumatoid arthritis [Y / N] and baseline DAS28-ESR as a covariate. Fixed effects were based on IRT.

[b] For the FDA: MSB11456 was considered equivalent to EU-RoActemra if the 90% confidence interval was included in the equivalence interval of [-0.6, 0.5]. For the EMA: MSB11456 was considered equivalent to EU-RoActemra if the 95% confidence interval was included in the equivalence interval of [-0.6, 0.6].

Note: Patients with a missing Week 24 value were not included.

Tipping Point Analysis

To assess the robustness of the missing at random assumption for the primary estimand, a tipping point analysis was also performed, based on the same analysis of covariance model as for the primary analysis. Missing data were imputed by means of the multiple imputation approach of the primary estimand, with imputed values adjusted with a sequence of shift values for DAS28-ESR change from baseline at Week 24 of between -3 and 3, separately by treatment.

Tipping points were identified in both the analysis for the FDA and the analysis for the EMA. In the analysis for the EMA, no tipping points were identified. The applicant states that the tipping point identified for the FDA analysis was the most extreme case possible and seems implausible considering the results of Estimand 1.2 which addressed the worst case scenario of returning to baseline.

Subgroup analyses

By previous Exposure to Biologic Treatment and by COVID19 Vaccination Status

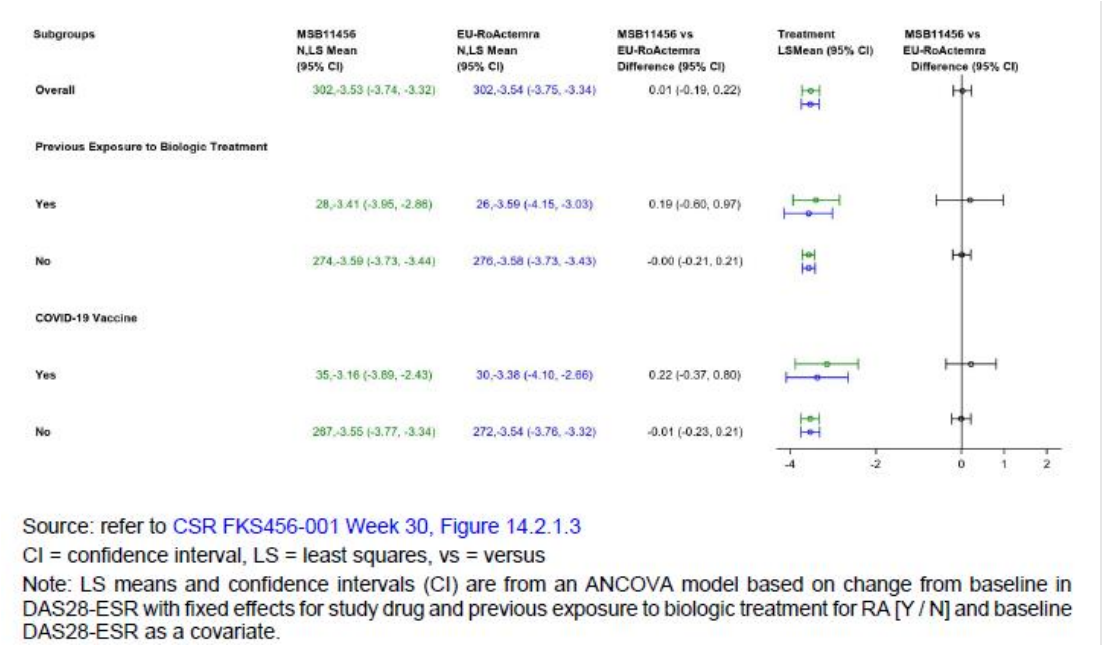
Subgroup analysis by Previous Exposure to Biologic Treatment for Rheumatoid Arthritis i.e., change of baseline DAS28-ESR at Week 24 in the ITT Analysis Set is presented in

Figure 9 DAS-ESR Change from Baseline at Week 24, Subgroup Analysis. The subgroup with previous exposure to biologic treatment for rheumatoid arthritis consisted of 29 patients in MSB11456 and 26 patients in EU-Roactemra group respectively.

Stratified analysis by COVID19 Vaccination status is also shown in Figure 9. The COVID 19 vaccinated consisted of 35 patients in the MSB11456 group and 30 patients in the EU-RoActemra group.

For the above subgroup analyses, similar results were observed in the PP Analysis Set as in the ITT Analysis Set.

Figure 9 DAS-ESR Change from Baseline at Week 24, Subgroup Analysis



Source: refer to CSR FKS456-001 Week 30, Figure 14.2.1.3
CI = confidence interval, LS = least squares, vs = versus
Note: LS means and confidence intervals (CI) are from an ANCOVA model based on change from baseline in DAS28-ESR with fixed effects for study drug and previous exposure to biologic treatment for RA [Y / N] and baseline DAS28-ESR as a covariate.

By Antidrug Antibody (ADA) Status and by Neutralising Antibody (NAb) Status

DAS28-ESR change from baseline at Week 24 was to be summarised by ADA status and by NAb in the ITT Analysis Set and PP Analysis Set. The applicant states that these analyses were not done because the ADA-negative subgroup category and the NAb-positive group included fewer than 10% of patients in the respective analysis population the planned analyses. See Table 27 for the ADA overall status results. As presented below, the proportions of ADA incidence at week 24 was 76.3% (209/274) in the MSB11456 group and 68.6% (194/283) in the EU-RoActemra group.

Table 27 ADA and Nab incidence, and ADA titre by time point, core period (safety analysis set)

Time Point	ADA incidence % (n/N*)		ADA titer Median	
	MSB11456 (N=302)	EU-RoActemra (N=302)	MSB11456 (N=302)	EU-RoActemra (N=302)
Overall	96.0 (287/299)	96.3 (290/301)	120.0	120.0
Baseline	6.6 (20/302)	8.3 (25/302)	60.0	60.0
Week 2	87.1 (250/287)	88.7 (258/291)	60.0	60.0
Week 12	79.0 (222/281)	74.3 (217/292)	120.0	120.0
Week 24	76.3 (209/274)	68.6 (194/283)	120.0	120.0

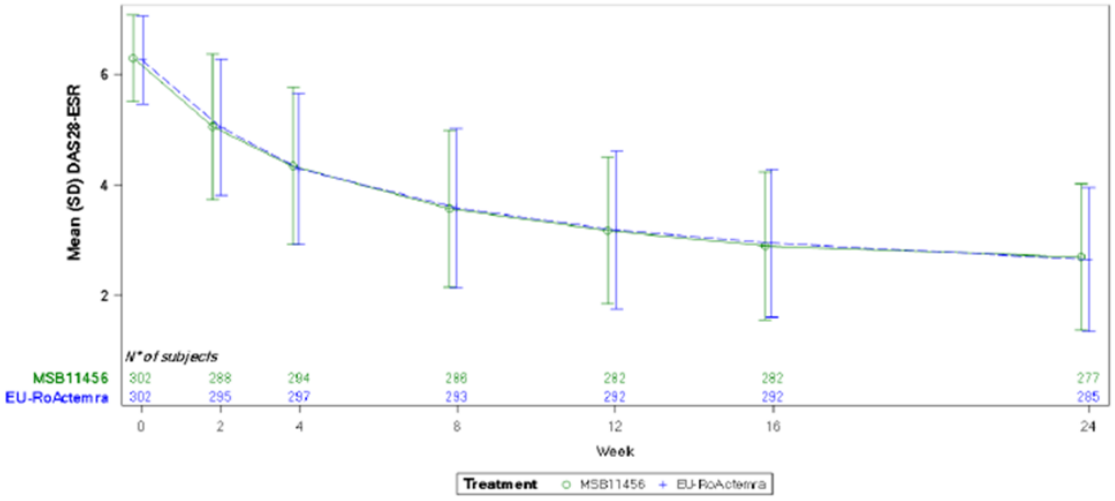
Time Point	ADA titer Geometric Mean (min, max)		NAb incidence % (n/N*)	
	MSB11456 (N=302)	EU-RoActemra (N=302)	MSB11456 (N=302)	EU-RoActemra (N=302)
Overall	106.1 (60,15360)	104.1 (60,122880)	8.4 (25/299)	11.0 (33/301)
Baseline	71.4 (60,960)	130.4 (60,1920)	0	0
Week 2	81.2 (60,1920)	88.1 (60,15360)	3.8 (11/287)	3.4 (10/291)
Week 12	113.8 (60,960)	123.1 (60,122880)	2.5 (7/281)	3.8 (11/292)
Week 24	137.5 (60,15360)	103.4 (60,1920)	2.9 (8/274)	4.9 (14/283)

ADA = antidrug antibody, n = number of patients with positive status, EU-RoActemra = European Union–approved RoActemra, N* = number of patients with a valid ADA result, NAb = neutralizing antibody. N is the number of patients in the Safety Analysis Set
Titer: Reciprocal of total sample dilution factor, including the assay minimum required dilution
Overall: Determined across all time points except Baseline (predose).
Source: Listing 16.2.6.8, Dataset: ADIS, Program: t-ada-nab-intp-cp.sas, Output: T-14-02-08-01-01-ada-nab-cp.rtf, Generated on: 28FEB2022 at 09:49

DAS28-ESR Mean Change from Baseline at All Assessment Visits up to Week 30

DAS28-ESR mean absolute change from baseline was determined at all assessment visits except Week 1 (i.e., at Weeks 2, 4, 8, 12, 16, 24, and 30). The LS mean decrease in DAS28-ESR from baseline and at all assessment visits (except week 1) are presented in Figure 10. Overall, the LS mean decreases from baseline in DAS28-ESR at Week 24 were observed from the entire throughout all visits and sustained to Week 30 in the MSB11456 and EU-RoActemra groups. The DAS28-ESR mean changes from baseline at Week 30 were similar in both the MSB11456 and EU-RoActemra groups, as indicated by the 95% CIs for the difference in change from baseline between groups.

Figure 10 Mean (SD) DAS28-ESR over time -Core Treatment Period (ITT)



Key Secondary Estimand (ACR20 Response Rate at Week 24)

Key Secondary Estimand 2.0 (ACR20 ITT)

ACR20 response at Week 24 in the ITT Analysis Set (Key Secondary Estimand 2.0) using last observation carried forward (LOCF) is summarised in Table 28. In brief the proportion of patients reaching ACR20 response at week 24 was 80.75% in the MSB11456 group and 84.77 % in the EU-RoActemra group. The difference (%) in response rate was -3.94 (95%CI -9.97 to 2.11).

Table 28 ACR20 response at week 24-Key Secondary Estimand 2.0-LOCF (ITT analysis set)

Variable Statistic	MSB11456 (N=302)	EU-RoActemra (N=302)	Difference MSB11456 – EU-RoActemra (N=604)
Responder[a] [n (%)]	244 (80.79)	256 (84.77)	
Non-Responder [n (%)]	58 (19.21)	46 (15.23)	
Number of Imputed Values	24	15	
Difference in % Response Rate			-3.94
95% Confidence Interval[b]			(-9.97, 2.11)

ACR20 = American College of Rheumatology (ACR) 20% improvement in ACR core set measures, CRP = C-reactive protein, ESR = Erythrocyte Sedimentation Rate, EU-RoActemra = European Union–approved RoActemra, ITT = Intent-to-Treat, LOCF = last observation carried forward

[a] An ACR20 responder was defined as a 20% improvement in the 66 swollen and 68 tender joint counts plus a 20% improvement in at least 3 of these 5 measures: Patient's Global Assessment of Disease Activity, Patient's Assessment of Arthritic Pain, Health Assessment Questionnaire – Disability Index, Physician's Global Assessment of Disease Activity, and CRP or ESR. Missing ACR response data at Week 24 were imputed using LOCF.

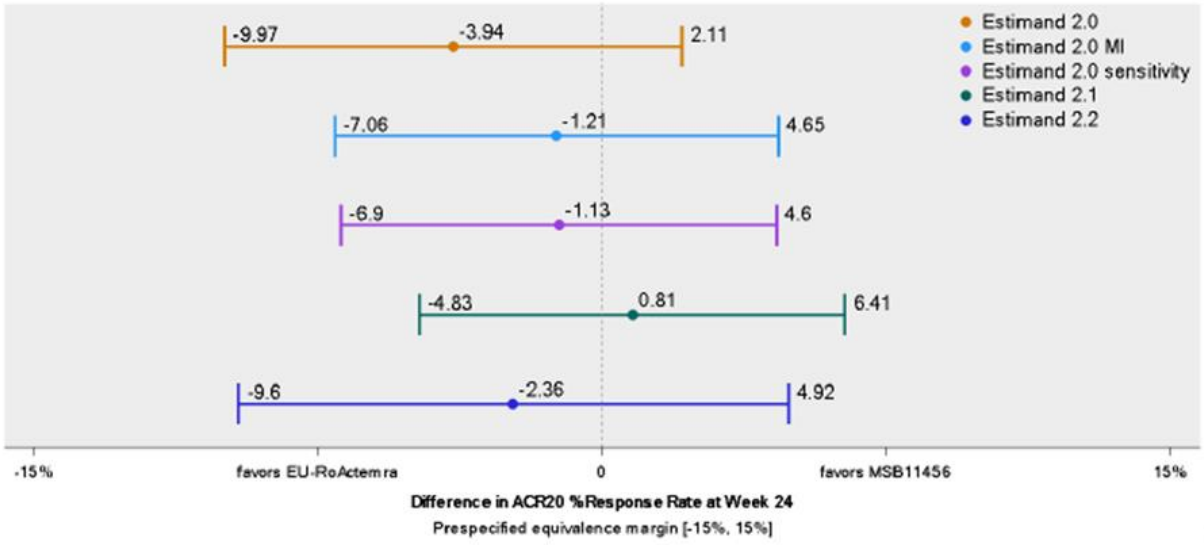
[b] The stratified difference in ACR20 response rate at Week 24 was analyzed using a 95% stratified Newcombe confidence interval adjusting for the stratification factor previous exposure to biological treatment for rheumatoid arthritis. The equivalence margin was [-15%, 15%].

Source: Listing 16.2.6.2, Dataset: ADEFF, Program: t-14-02-03-01-01.sas, Output: T-14-02-03-01-01-acr-sec-esti.rtf, Generated on: 09FEB2022 at 02:12

Supportive Estimands 2.1, 2.2, and sensitivity analyses of ACR20 response rate at week 24

Supportive analyses of the ACR20 response rate at Week 24 i.e., supportive Estimand 2.1 using the PP Analysis Set and supportive Estimand 2.2 using the hypothetical return to baseline ITT analysis) as well as sensitivity analyses (no imputation of missing data, multiple imputation of data, tipping point analysis) are presented in Figure 11.

Figure 11 Estimand 2: 95% CI for the Difference at Week 24 in ACR20 response rate between MSB11456 and EU-RoActemra



Source: refer to CSR FKS456-001 Week 30, Table 14.2.3.1.1, Table 14.2.3.4, Table 14.2.3.1.2, Table 14.2.3.2.1 and Table 14.2.3.3

ACR20 = 20% improvement in American College of Rheumatology Core Set Measurement, CI = confidence interval, MI = multiple imputation

Note: Estimand 2.0 sensitivity is the sensitivity analysis with no imputation. Estimand 2.0 MI is the sensitivity analysis with multiple imputation.

The difference in ACR20 response rate at Week 24 was analyzed using a 95 % Newcombe confidence interval adjusting for previous exposure to biologic treatment for RA [Y/N].

Subgroup analyses of ACR20 response rate at week 24

Subgroup analyses of the ACR20 response rate at Week 24 were performed by previous exposure to biologic treatment for RA and by previous COVID-19 vaccination status. According to the applicant, largely similar results were observed for the PP Analysis Set as for the ITT Analysis Set. The difference (%) in response rate was quite high especially among those with prior biological therapy i.e., -5.72 (-27.03 to 16.58) and among those that had received COVID19 vaccination i.e., -7.25 (-24.16 to 10.65) Of note the analyses were hampered by low precision.

Ancillary analyses

Supportive Estimand 3.0: Early DAS28-ESR Change from Baseline at Week 12 and remaining explorative analysis

The result of the analysis of the supportive Estimand 3.0 (i.e., the same attributes as Primary Estimand 1.0, except that Week 24 was replaced by Week 12 in all relevant attributes' description to investigate early treatment effects) was overall similar as that of the primary estimand. The results of the statistical analyses of supportive estimands 3.1 (early DAS28-ESR, PP) and supportive estimands 3.2 (early DAS28-ESR hypothetical continuing as PP, ITT) as well as a sensitivity analysis of supportive Estimand 3.0 with no imputation were overall similar to those of the supportive Estimand 3.0 in the ITT Analysis Set.

Likewise, didn't the results of the remaining explorative analyses show any substantially different results as compared to the main analyses.

Efficacy after week 24

The comparisons of efficacy between the MSB11456 and RMP groups after week 24 were based on the data for the Overall Period (from Week 1 up to Week 52). The exploration of the effects of a single-treatment transition in the RMP to MSB11456 group compared with the MSB11456 group and compared with the RMP group, is based on the data for the Extended Period (from Week 24/extended baseline up to Week 52). DAS28-ESR repeated measures analyses for change from baseline (i.e., primary endpoint) are summarised for the Overall Period in Table 29 (ITT Analysis Set). The results were overall in line with the 24-weeks results. A substantially similar result was observed also for the secondary endpoint/estimands.

Table 29 DAS28-ESR – Repeated Measures Analysis for Change from Baseline at Week 52 – Overall Period (ITT Analysis Set)

Time Point Variable Statistic	MSB11456 (N=302)	EU-RoActemra (N=163)	EU-RoActemra/ MSB11456 (N=139)
Baseline			
n (missing)	302 (0)	163 (0)	139 (0)
Mean (std)	6.28 (0.787)	6.18 (0.842)	6.34 (0.729)
Median	6.2	6.2	6.3
Min, Max	3.0, 8.3	3.3, 8.1	4.3, 8.0
Week 52			
n (missing)	248 (54)	126 (37)	126 (13)
Mean (std)	2.20 (1.290)	2.21 (1.255)	2.18 (1.136)
Median	2.0	2.2	2.2
Min, Max	0.2, 8.5	0.0, 7.2	0.3, 6.1
Change from Baseline to Week 52			
n (missing)	248 (54)	126 (37)	126 (13)
Mean (std)	-4.12 (1.329)	-3.96 (1.263)	-4.17 (1.155)
Median	-4.3	-4.1	-4.1
Min, Max	-7.6, 0.3	-7.1, 0.2	-6.5, 0.2
LS Mean (SE)[a]	-4.00 (0.093)	-3.80 (0.120)	-4.05 (0.121)
95% Confidence Interval[a]	(-4.18, -3.81)	(-4.04, -3.57)	(-4.29, -3.82)
Difference in Change from Baseline			
MSB11456 – EU-RoActemra			
LS Mean Difference (SE)[a]	-0.19 (0.134)		
95% Confidence Interval[a]	(-0.45, 0.07)		
MSB11456 – EU-RoActemra/MSB11456			
LS Mean Difference (SE)[a]	0.06 (0.136)		
95% Confidence Interval[a]	(-0.21, 0.33)		
EU-RoActemra/MSB11456 – EU-RoActemra			
LS Mean Difference (SE)[a]			-0.25 (0.155)
95% Confidence Interval[a]			(-0.56, 0.06)

DAS28-ESR = Disease Activity Score-28 Erythrocyte Sedimentation Rate, EU-RoActemra = European Union-approved RoActemra, ITT = Intent-to-Treat, LS = least squares, SE = standard error, std = standard deviation
[a] LS means, standard errors, and confidence intervals were from a mixed-effect repeated measures model assuming an unstructured covariance matrix with treatment, visit, treatment-by-visit interaction, previous exposure to biologic treatment for rheumatoid arthritis (Y/N) included as factors and baseline DAS28-ESR from the Core Period as a covariate.

Summary of main efficacy results

Table 30 summarises the main efficacy results from Study FKS456-001 supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30 Summary for efficacy in trial (FKS456-001)

Title: A Randomized, Double-blind, Multiple-dose, Parallel-group, Two-arm Study to Evaluate the Efficacy, Safety, and Immunogenicity of MSB11456 Compared to European Union–approved RoActemra® in Patients with Moderately to Severely Active Rheumatoid Arthritis (APTURA I Study)		
Study identifier	Protocol number: FKS456-001, EudraCT number: 2019-004369-42	
Design	This was a multicentre, randomised (1:1), active-controlled, double-blind, multiple fixed-dose, multinational, two-arm, parallel-group study to compare the efficacy, safety and immunogenicity of the proposed biosimilar candidate MSB11456 versus EU-approved RoActemra in patients with moderately to severely active rheumatoid arthritis. Randomisation was stratified by previous exposure to biologic treatment for rheumatoid arthritis (yes/no). At the end of Week 24 Visit, after all planned assessments had been conducted and the investigator had confirmed that the study drug did not need to be discontinued (Refer to Module 5.3.5.1 FKS456-001 CSR Appendix 16.1.1 - Protocol Section 6.3 for criteria for patient withdrawal), patients were re-randomised. Patients initially randomised to the MSB11456 group were re-assigned to the same treatment with a probability of 1. Patients initially randomised to the EU-approved RoActemra group were randomly assigned in a 1:1 ratio to receive either MSB11456 or EU-approved RoActemra. This extension Phase included a 28-weeks period of double-blind treatment, followed by 12 weeks of safety follow-up.	
	Duration of main phase:	24 weeks (also referred as Core Treatment Period)
	Duration of Run-in phase:	4 weeks (also referred as Screening Period)
	Duration of Extension phase:	40 weeks, including - 28 weeks of treatment (also referred as Extended Treatment Period) - 12 weeks of safety follow-up
Hypothesis	Equivalence	
Treatments groups	MSB11456	Tocilizumab biosimilar candidate, weekly subcutaneous injections (162 mg) for a duration of 52 weeks, number of randomised patients: n=302 in main
	EU-RoActemra	EU-RoActemra, weekly subcutaneous injections (162 mg) for a duration of maximum 52 weeks, number of randomised patients: n=302 in main phase, n= 137 in Extension phase.

	EU-RoActemra/ MSB11456		EU-RoActemra, weekly subcutaneous injections (162 mg) for a duration of 24 weeks in main Phase, followed by Tocilizumab biosimilar candidate, weekly subcutaneous injections (162 mg) during 28 weeks in Extension phase, n= 139.
Endpoints and definitions	Primary endpoint	DAS28-ESR Change from baseline to Week 24	Change from baseline at Week 24 in Disease Activity Score 28-Erythrocyte Sedimentation Rate
	Secondary endpoint	ACR20 at week 24	ACR20 (20% improvement in ACR Core Set Measurements) response at Week 24
	Secondary endpoint	DAS28-ESR Change from baseline to Week 12	Change from baseline at Week 12 in Disease Activity Score 28-Erythrocyte Sedimentation Rate
Database lock	15 December 2021		
Results and Analysis			
Analysis description	**Primary Analysis of the primary endpoint: DAS28-ESR Change from baseline at Week 24 (pre-specified)**		
Analysis population and time point description	Intent to Treat Analysis Set: includes all randomised patients Week 24		

Descriptive statistics and estimate variability	Treatment group	MSB11456	EU-RoActemra
	Number of subjects	302	302
	DAS28-ESR Change from baseline to week 24 (LS Mean)	-3.53	-3.54
	Standard Error (SE)	0.105	0.105
	DAS28-ESR Change from baseline to week 24 (95% Confidence Interval)	(-3.74, -3.32)	(-3.75, -3.34)
Effect estimate per comparison	Primary endpoint	Comparison groups	Difference MSB11456 – EU-RoActemra
		Difference between groups (Standard error)	0.01 (0.104)
		95% Confidence Interval	(-0.19, 0.22)
		P-value	N/A

Notes	MSB11456 was considered equivalent to EU-RoActemra as the 95% confidence interval for the difference was included in the predefined equivalence interval of [-0.6, 0.6]. Least Square (LS) means, standard errors (SE), and confidence intervals are from an Analysis of Covariance (ANCOVA) model based on change from baseline in DAS28-ESR with fixed effects for treatment and previous exposure to biologic treatment for rheumatoid arthritis, and baseline DAS28-ESR as a covariate. The comparison between the two treatment groups was made as per randomised treatment policy regardless of potential treatment discontinuation or background therapy change. A multiple imputation approach was used for 25 and 17 patients with no endpoint data in MSB11456 and EU-RoActemra treatment group, respectively. For a full description of Estimand 1.0, refer to the SAP in Module 5.3.5.1 FKS456-001 CSR, appendix 16.1.9, section 12.5.4.		
Analysis description	**Supportive analysis of the primary endpoint: DAS28-ESR Change from baseline at Week 24 (pre-specified)**		
Analysis population and time point description	Per Protocol Analysis Set: includes all randomised patients who completed the main phase with no clinically important protocol deviations and with at least 80% compliance in study treatment and Methotrexate. Week 24		
Descriptive statistics and estimate variability	Treatment group	MSB11456	EU-RoActemra
	Number of subjects with non missing data	243	251
	DAS28-ESR Change from baseline to week 24	-3.72	-3.68
	Standard Error (SE)	0.102	0.102
	DAS28-ESR Change from baseline to week 24 (95% Confidence Interval)	(-3.92, -3.52)	(-3.88, -3.48)
Effect estimate per comparison	Primary endpoint	Comparison groups	Difference MSB11456 – EU-RoActemra
		Difference between groups (Standard error)	-0.04 (0.103)
		95% Confidence Interval	(-0.24, 0.17)
		P-value	N/A

Notes	MSB11456 was considered equivalent to EU-RoActemra as the 95% confidence interval for the difference was included in the predefined equivalence interval of [-0.6, 0.6]. Least Square (LS) means, standard errors (SE), and confidence intervals are from an Analysis of Covariance (ANCOVA) model based on change from baseline in DAS28-ESR with fixed effects for treatment and previous exposure to biologic treatment for rheumatoid arthritis and baseline DAS28-ESR as a covariate. For a full description of Estimand 1.1, refer to the SAP in Module 5.3.5.1 FKS456-001 CSR, appendix 16.1.9, Section 12.5.4.3. Reasons for exclusion from the Per Protocol Analysis Set across study treatments were treatment compliance < 80% (11.4%, n=69), no Week 24 visit (10.9%, n=66), Methotrexate compliance < 80% (7.1%, n=43), clinically important protocol deviation (1.5%, n=9).		
Analysis description	**Analysis of the secondary endpoint ACR20 at week 24 (pre-specified)**		
Analysis population and time point description	Intent to Treat Analysis Set: includes all randomised patients Week 24		
Descriptive statistics and estimate variability	Treatment group	MSB11456	EU-RoActemra
	Number of subjects	302	302
	ACR20 response rate at week 24	80.79 %	84.77 %
Effect estimate per comparison	Secondary endpoint	Comparison groups	Difference MSB11456 – EU-RoActemra
		Difference in % response rate between groups	-3.94
		95% Confidence Interval	(-9.97, 2.11)
		P-value	N/A
Notes	MSB11456 was considered equivalent to EU-RoActemra as the 95% confidence interval for the difference was included in the predefined equivalence interval of [-15%, 15%]. The difference in ACR20 response rate at Week 24 was analysed using a 95% stratified Newcombe confidence interval adjusting for the randomisation stratification factor (previous exposure to biological treatment for rheumatoid arthritis). The comparison between the two treatment groups was made as per randomised treatment policy regardless of potential treatment discontinuation or background therapy change. Last observation carried forward was used for 24 and 15 patients with no endpoint data at Week 24 for MSB11456 and EU-RoActemra, respectively.		
Analysis description	**Supportive analysis of the secondary endpoint ACR20 at week 24 (pre-specified)**		

Analysis population and time point description	Per Protocol Analysis Set: includes all randomised patients who completed the main phase with no clinically important protocol deviations and with at least 80% compliance in study treatment and Methotrexate. Week 24		
Descriptive statistics and estimate variability	Treatment group	MSB11456	EU-RoActemra
	Number of subjects with no missing data	244	253
	ACR20 response rate at week 24	89.34 %	88.54 %
Effect estimate per comparison	Secondary endpoint	Comparison groups	Difference MSB11456 – EU-RoActemra
		Difference in % response rate between groups	0.81
		95% Confidence Interval	(-4.83, 6.41)
		P-value	N/A
Notes	MSB11456 was considered equivalent to EU-RoActemra as the 95% confidence interval for the difference was included in the predefined equivalence interval of [-15%, 15%]. The difference in ACR20 response rate at Week 24 was analysed using a 95% stratified Newcombe confidence interval adjusting for the randomisation stratification factor (previous exposure to biological treatment for rheumatoid arthritis).		
Analysis description	**Analysis of the secondary endpoint: DAS28-ESR Change from baseline at Week 12 (pre-specified)**		
Analysis population and time point description	Intent to Treat Analysis Set: includes all patients randomised Week 12		
Descriptive statistics and estimate variability	Treatment group	MSB11456	EU-RoActemra
	Number of subjects	302	302
	DAS28-ESR Change from baseline to week 12 (LS Mean)	-3.13	-3.12
	Standard Error (SE)	0.104	0.104
	DAS28-ESR Change from baseline to week 12 (95% Confidence Interval)	(-3.33, -2.92)	(-3.32, -2.91)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Difference MSB11456 – EU-RoActemra

		Difference between groups (Standard error)	-0.01 (0.103)
		95% Confidence Interval	(-0.21, 0.19)
		P-value	N/A
Notes	Least Square (LS) means, standard errors and confidence intervals are from an Analysis of Covariance (ANCOVA) model based on change from baseline in DAS28-ESR at Week 12 with fixed effects for study drug and previous exposure to biologic treatment for Rheumatoid Arthritis, and baseline DAS28-ESR as a covariate. For a full description of the analysis of Estimand 3.0, refer to the SAP in Module 5.3.5.1 FKS456-001 CSR, appendix 16.1.9, Section 12.5.6.1.		
Analysis description	**Supportive analysis of the secondary endpoint DAS28-ESR Change from baseline at Week 12 (pre-specified)**		
Analysis population and time point description	Per Protocol Analysis Set: includes all randomised patients who completed the main phase with no clinically important protocol deviations and with at least 80% compliance in study treatment and Methotrexate. Week 12		
Descriptive statistics and estimate variability	Treatment group	MSB11456	EU-RoActemra
	Number of subjects with non missing data	243	252
	DAS28-ESR Change from baseline to week 12 (LS Mean)	-3.23	-3.17
	Standard Error (SE)	0.110	0.110
	DAS28-ESR Change from baseline to week 12 (95% Confidence Interval)	(-3.45, -3.02)	(-3.38, -2.95)
Effect estimate per comparison	Secondary endpoint	Comparison groups	Difference MSB11456 – EU-RoActemra
		Difference between groups (Standard error)	-0.07 (0.111)
		95% Confidence Interval	(-0.28, 0.15)
		P-value	N/A

Notes	Least Square (LS) means, standard errors and confidence intervals are from an Analysis of Covariance (ANCOVA) model based on change from baseline in DAS28-ESR with fixed effects for study drug and previous exposure to biologic treatment for Rheumatoid Arthritis, and baseline DAS28-ESR as a covariate. For a full description of the analysis of Estimand 3.1, refer to the SAP in Module 5.3.5.1 FKS456-001 CSR, appendix 16.1.9, Section 12.5.6.2.

2.6.5.3. Clinical studies in special populations

Not applicable for a biosimilar.

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)

Not applicable

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Study FKS456-001 was a randomised, double-blind, multiple-dose, parallel-group clinical study conducted in patients with moderately to severely active RA who have experienced an inadequate clinical response to at least one DMARD (either synthetic or biologic) and are currently receiving a stable dose of methotrexate. The overall aim is to evaluate efficacy, safety, and immunogenicity similarity of MSB11456 to EU-RoActemra administered as a weekly injection of 162 mg subcutaneously.

The study consists of a Screening period, a double-blind 24-week Core Treatment Period followed by an additional 28-week double-blind Extended Treatment Period and a 12-week Safety Evaluation Period. This original submission covered efficacy, safety, immunogenicity and PK results up to Week 30, thus covering the 24-week Core Treatment Period and the first 6 weeks of the Extended Treatment Period. At the CHMP's request, the applicant submitted a new CSR including efficacy data up to Week 52 and additional safety data including immunogenicity up until Week 63, see safety section for more details.

The choice of the indication (rheumatoid arthritis), the clinical setting (patients not adequately controlled with methotrexate or previous biological treatment), the primary and key secondary endpoints (DAS28-ESR and ACR20 at week 24) and the equivalence margin (± 15%) are in line with the CHMP guidance and were endorsed in CHMP Scientific Advice. The pre-specified equivalence margins of the primary efficacy estimand (DAS28-ESR at Week 24) set to [-0.6, 0.6] is also endorsed. Thus, the clinical model is considered sufficiently sensitive to enable the detection of differences between the two products.

The study objectives and the participants are overall acceptable. It should be noted that all patients were treated with concomitant methotrexate. This has potential impact on the extrapolation to indications where tocilizumab is intended for monotherapy, since concomitant methotrexate is expected to decrease the risk for immunogenicity. The time period for enrolment into the study and the included study sites and setting are also acknowledged. There is no concern about the amendments to the study protocol. The methods used for randomisation (including randomisation by

previous biologic treatment) and blinding are likewise acceptable. Patients who previously received 1 or 2 biologic treatments for rheumatoid arthritis were capped at 10% of the total study population.

Statistical methods

Scientific advice regarding the estimands, handling of missing data and analyses was given by the CHMP on 24 June 2021 (EMA/SA/0000060099). The advices given were mainly followed. Although the primary 24-week endpoint was accepted by CHMP, the importance of an earlier, potentially more sensitive, time point to confirm consistency across the study regarding the conclusion on biosimilarity was raised by the CHMP. An early efficacy estimand at week 12 has been defined to meet this requirement. This is endorsed.

The spectrum of analysis approaches described for DAS28 (one primary and three supportive/supplementary estimands, including sensitivity analyses) is seen to cover a sufficiently broad range of assumptions, allowing for assessment of robustness of conclusion drawn. The more conventional ITT and PP population analyses were performed as well as an approach to define a 'PP-like' estimand based on the full analyses set, which is endorsed.

For the key secondary endpoint (ACR20) the CHMP advised to use multiple imputation (MI) methods rather than single imputation methods. This advice was not followed in the primary analyses since LOCF, and non-responder imputations was used. MI is however introduced in sensitivity analyses which is endorsed. The different analyses provided is considered to cover a sufficiently broad range of assumptions also for this endpoint.

No multiple test procedure for secondary endpoints were planned or used in the study, making only the primary analysis formally type I error protected.

Results

Participants flow, protocol deviations

Of the 908 patients with RA screened, a total of 604 (302 in each treatment group) were randomised. All of these received study drug administered SC according to the randomised treatment and were included in the Safety Analysis Set.

The proportions of patients discontinuing study drug prior to Week 24 were 35 (11.6%) and 26 (8.6%) in the MSB11456 and EU-RoActemra groups respectively. The major reasons were, according to the applicant, AEs and consent withdrawal. Although the differences by treatment group were quite small, the reasons behind consent withdrawal were not entirely clear in the first submission. The applicant has in the second round presented the reasons for withdrawal. It is overall agreed that treatment discontinuation rate was relatively low and quite balanced across arms in the Core Period and the numerical differences between treatment groups observed were probably not related to differences between the treatment groups but instead considered a chance observation. Further, the high occurrence of major protocol deviations (PDs) in the ITT analysis set during the Core Treatment Period in both treatment groups has been clarified by the applicant displaying that the reasons for the high proportion of PDs were due to a very conservative definition of major protocol deviations. This included for example that both COVID-19 treatments and vaccinations were included as a prohibited medicine and thereby resulted in a PD. In the light of this very strict definition of PDs it is overall agreed with the applicant that the recorded major PDs did not impact data validity and integrity of the study.

Baseline characteristics

Demographic characteristics and baseline disease characteristics were overall balanced across treatment groups in the ITT Analysis Set. The two treatment groups were also largely balanced with respect to medical history and prior medication. Most of the included patients had high disease activity

at baseline according to multiple measures of disease activity. Disease activity were however equally distributed between the treatment groups. Of note, the proportion of patients with positive anti-drug antibodies (ADA) were lower (6.6 versus 8.3%) as was also the ADA titres (108 versus 252) in the MSB11456 versus the EU-RoActemra group.

Efficacy data and additional analyses

For the primary endpoint/primary estimand i.e., the absolute mean change of DAS28-ESR at 24 weeks was -3.53 (95% CI -3.74 to -3.32) for MSB11456 and -3.34 (95% CI -3.75 to -3.35) for EU-RoActemra. This corresponded to a LS mean difference of 0.01 (standard error 0.104) with a 95% CI of -0.19 to 0.22. The mean change of DAS28-ESR in both treatment groups is considered high and clinically relevant. The results support therapeutic equivalence of MSB11456 and EU-RoActemra with the 95% CIs for the LS mean differences in change from baseline between groups fully included within the respective predefined equivalence intervals. The results of the statistical analyses of supportive Estimand 1.1 (PP approach) and Supportive Estimand 1.2 and 1.3 (DAS28-ESR Hypothetical Return-to-Baseline PP and ITT respectively) were also supportive of therapeutic equivalence between the treatment arms. Likewise, the sensitivity (no imputation and tipping point) analyses supported the original findings in the analysis of the primary estimand. In subgroup analyses, i.e., stratifying for the previous exposure to biologic treatment for rheumatoid arthritis and for COVID19 vaccination status also showed largely similar results as the main analysis although with limited statistical precision.

In addition, the results from the explorative analyses of DAS28-ESR mean absolute change from baseline at all assessment visits except Week 1 (i.e., at Weeks 2, 4, 8, 12, 16, 24, and 30) also indicated similar efficacy in both treatment groups. The submitted results support the comparable efficacy between MSB11456 and RoActemra.

Of note, the number of missing values of the primary endpoint i.e., DAS28-ESR at week 24 is rather high (25 versus 17 in the MSB11456 and the EU-RoActemra group respectively). According to the applicant the main reason for missing on DAS28-ESR at Week 24 data was due to patients discontinuing prior to Week 24 and further that the impact of the missing data was minimal as the sensitivity analyses were in line with and support the primary analysis. This is acceptable.

The applicant states that prespecified subgroup analyses by ADA status and by NAb status were not performed because the ADA-negative subgroup category and the NAb positive subgroup respectively included fewer than 10% of the patients. Although this is overall agreed when looking at the entire study period, the proportions of ADA incidence at week 24 was 76.3% (209/274) in the MSB11456 group and 68.6% (194/283) in the EU-RoActemra group, see below for further reasoning on this.

The proportion of patients reaching the key secondary estimand (ACR20 response at week 24) was 80.75% in the MSB11456 group and 84.77 % in the EU-RoActemra group. The difference (%) in response rate was thus -3.94 (95% CI -9.97 to 2.11). Thus, the 95% confidence interval falls within the pre-defined equivalence margin of +/-15%.

The result of the analyses of the supportive estimands 2.1 and 2.2 as well as the sensitivity analyses were also overall similar to the main analysis of the key secondary estimand. This was also the case for the subgroup analyses. Again, the difference (%) in response rate was high especially among those with prior biological therapy, 5.72 (-27.03 to 16.58) and among those that had received COVID19 vaccination, -7.25 (-24.16 to 10.65). However, the interpretation of these subgroup analyses was hampered by small sample size.

At the CHMP's request, the applicant presented data on efficacy after week 24 based on the results for the Overall Period (from Week 1 up to Week 52). The results were overall in line with the 24-weeks results. A substantially similar result was observed also for the secondary endpoint/estimands.

Given the importance of ADA/ immunogenicity for the assessment, the applicant was asked to provide descriptive data regarding the primary and key secondary endpoints in the two treatment groups by ADA and NAb status. Taken together this data (provided in the second round) show a substantially similar response with respect to the primary and secondary endpoints by ADA and by Nab in the EU-RoActemra group and the MSB11456 group respectively. This was true both for the core period (24-week), the overall period and when presenting data on primary and secondary endpoints by each visit. Of note the proportions of ADA negative and Nab positive patients respectively are very few, making robust conclusions difficult to draw.

For further discussion on the impact of ADA on drug levels and efficacy, please refer to section2.6.8. (Clinical safety).

2.6.7. Conclusions on the clinical efficacy

The pivotal study FKS456-001 including 604 subjects with RA randomised 1:1 to either MSB11456 or EU-RoActemra comprised a double-blind 24-week Core Treatment Period followed by an additional 28-week double-blind Extended Treatment Period and a 12-week Safety Evaluation Period. Efficacy data up until week 52 was submitted with this application and showed evidence of therapeutic equivalence between MSB11456 and EU-RoActemra in this sensitive clinical model of RA, and therefore, supports biosimilarity with respect to efficacy.

2.6.8. Clinical safety

The clinical safety data supporting a similar clinical profile of MSB11456 relative to the reference product (Ro)Actemra for the SC route of administration is drawn primarily from 2 clinical studies: 1) the comparative pivotal pharmacokinetic (PK)/pharmacodynamic (PD) Study MS200740-0001 that randomised 695 healthy subjects and 2) the comparative pivotal safety and efficacy Study FKS456-001 that randomised 604 subjects with rheumatoid arthritis (see Table 31). Further safety information of MSB11456 is provided by Study FKS456-003 comparing the administration of MSB11456 by PFS and AI in 100 healthy volunteers.

Evidence for a similar profile in terms of product safety when administered IV is primarily provided by Study FKS456-002.

2.6.8.1. Patient exposure

During the clinical development of MSB11456, a total of 834 subjects received at least one dose of MSB11456. Of those, the study drug was administered by SC injection in 772 subjects including 139 patients who have been switched from EU-RoActemra to MSB11456, and by IV infusion in 62 subjects (Table 31).

Table 31. Number of subjects receiving at least one dose of study drug

	Number of Subjects					
	IV administration		SC administration			
	MSB11456 8 mg/kg	US-Actemra 8 mg/kg	MSB11456 162 mg	EU-RoActemra 162 mg	EU-RoActemra/ MSB11456 162 mg	US-Actemra 162 mg
Studies in RA patients						
FKS456-001	-	-	302*	163**	139***	-
Studies in healthy subjects						
MS200740-0001	-	-	231	225	-	229
FKS456-002	62	66	-	-	-	-
FKS456-003			100			
Total	**62**	**66**	**633**	**388**	**139**	**229**

* The number corresponds to the MSB11456 arm only, switch subjects are not counted here even if they received at least one dose of MSB11456 at the Extended Period

** subjects who had received EU-RoActemra in the Overall Period

*** the number corresponds to subjects who had received EU-RoActemra in the Core Period but have been switched to MSB11456 in the Extended Period

Source: refer to CSR MS200740-0001, CSR FKS456-001 (w55), CSR FKS456-002, and CSR FKS456-003

IV = intravenous; RA = rheumatoid arthritis; SC = subcutaneous

In the pivotal study FKS456-001, a total of 441 randomised patients with rheumatoid arthritis were exposed to at least 1 injection of MSB11456. Overall, from Day 1 to Week 52 the mean exposure was 45.34 (±14.560) weeks in the MSB11456 group, 44.30 (±15.424) weeks in the EU-RoActemra group and 49.48 (±6.962) in the EU-RoActemra-to-MSB11456 group.

2.6.8.2. Adverse events

PK study MS200740-0001

AE was reported by 76.6% of subjects in the MSB11456 group, 69.0% in the US-Actemra group, and 74.7% in the EU-RoActemra group. Injection site reactions were slightly more frequent in the MSB11456 group (18/231 patients, 7.8%) than in the EU-RoActemra group (12/225 patients, 5.3%).

Table 32. Summary of adverse events in Study MS200740-0001

	Number of subjects (%) and number of events			
	MSB11456 (N=231)	**US-Actemra (N=229)**	**EU-RoActemra (N=225)**	**Overall (N=685)**
Any TEAE	177 (76.6) 399	158 (69.0) 405	168 (74.7) 387	503 (73.4) 1191
Any drug-related TEAEs	59 (25.5) 82	46 (20.1) 60	50 (22.2) 63	155 (22.6) 205
Any SAE	3 (1.3) 3	1 (0.4) 1	1 (0.4) 1	5 (0.7) 5
Any drug-related SAE	2 (0.9) 2	1 (0.4) 1	1 (0.4) 1	4 (0.6) 4
Any TEAE ≥ Grade 3	2 (0.9) 2	1 (0.4) 1	1 (0.4) 1	4 (0.6) 4
Any drug-related TEAE ≥ Grade 3	1 (0.4) 1	1 (0.4) 1	1 (0.4) 1	3 (0.4) 3
Death	0	0	0	0
AE leading to termination of study	0	0	0	0
AESI	19 (8.2) 24	3 (1.3) 4	13 (5.8) 18	35 (5.1) 46

Source: refer to CSR MS200740-0001, Table 15.3.1.1.
AE = adverse event, AESI = adverse event of special interest, SAF = safety analysis set, SAE = serious adverse event, TEAE = treatment-emergent adverse event

Table 33. Summary of AESIs in Study MS200740-0001

	Number of subjects (%) and number of events			
	MSB11456 (N=231)	**US-Actemra (N=229)**	**EU-RoActemra (N=225)**	**Total (N=685)**
Any AESI	19 (8.2) 24	3 (1.3) 4	13 (5.8) 18	35 (5.1) 46
General disorders and administration site conditions	**18 (7.8) 23**	**3 (1.3) 4**	**12 (5.3) 17**	**33 (4.8) 44**
Injection site erythema	15 (6.5) 15	3 (1.3) 3	12 (5.3) 12	30 (4.4) 30
Injection site pruritus	5 (2.2) 5	0	3 (1.3) 3	8 (1.2) 8
Injection site pain	2 (0.9) 2	0	1 (0.4) 1	3 (0.4) 3
Injection site swelling	1 (0.4) 1	1 (0.4) 1	1 (0.4) 1	3 (0.4) 3
Infections and infestations	**1 (0.4) 1**	**0**	**1 (0.4) 1**	**2 (0.3) 2**
Appendicitis perforated	1 (0.4) 1	0	1 (0.4) 1	2 (0.3) 2

Source: refer to CSR MS200740-0001, Tables 15.3.1.7
AESI = adverse event of special interest, SAF = safety analysis set

IV PK study FKS456-002

In the IV study FKS456-002, TEAEs occurred more frequently in the MSB11456 group (61.3%) than in the US-Actemra group (57.6%). Infusion site reactions were slightly more frequent in the MSB11456 group (4.8%) than in the US-Actemra group (3.0%).

Table 34. Summary of AEs of Study FKS456-002 (SAF)

TEAE category	Number of subjects (%) and number of events		
	MSB11456-IV (N=62)	US-Actemra-IV (N=66)	Total (N=128)
Any TEAEs	38 (61.3) 66	38 (57.6) 65	76 (59.4) 131
Subjects with worst grade of TEAE in each of the following categories			
Mild TEAE (CTCAE Grade 1)	10 (16.1) 13	18 (27.3) 28	28 (21.9) 41
Moderate TEAE (CTCAE Grade 2)	7 (11.3) 9	6 (9.1) 11	13 (10.2) 20
Severe TEAE (CTCAE Grade 3)	16 (25.8) 19	12 (18.2) 14	28 (21.9) 33
Life-threatening TEAE (CTCAE Grade 4)[a]	5 (8.1) 5	2 (3.0) 2	7 (5.5) 7
Death (CTEAE Grade 5)	0	0	0
Any drug-related TEAE	21 (33.9) 26	16 (24.2) 26	37 (28.9) 52
Any infusion site reaction	3 (4.8) 5	2 (3.0) 3	5 (3.9) 8
Any SAE	0	0	0
Any TEAE of special interest	0	0	0
Any TEAE leading to death	0	0	0
Any TEAE leading to study drug discontinuation	0	0	0

Source: refer to CSR FKS456-002, Table 14.3.1.1

[a] These AEs were graded applying NCI-CTCAE Version 5.0 (decreased neutrophil counts <0.50·10^9/L). The investigator did not consider any of these TEAEs either severe or life-threatening from a medical perspective and did not report these TEAEs as SAEs.

AE = adverse event, AESI = adverse events of special interest, CTCAE = common terminology criteria for adverse events, IV = intravenous, N = number of subjects, SAE = serious adverse event, TEAE = treatment-emergent adverse event, SAF = safety analysis set.

Prefilled syringe vs autoinjector study FKS456-003

A summary of AEs in study FKS456-003 is shown below.

Table 35.Summary of AEs of Study FKS456-003 (SAF)

TEAE category	Number of subjects (%) and number of events		
	MSB11456 AI (N=97)	MSB11456 PFS (N=94)	Overall (N=100)
Any TEAE	39 (40.2) 68]	40 (42.6) 55	53 (53.0) 123
Subjects with worst grade of TEAE in each of the following categories			
Grade 1 or Mild TEAE	16 (16.5)	11 (11.7)	16 (16.0)
Grade 2 or Moderate TEAE	17 (17.5)	26 (27.7)	30 (30.0)
Grade 3 or Severe TEAE	5 (5.2)	3 (3.2)	6 (6.0)
Grade 4 or Life-threatening TEAE[a]	1 (1.0)	0	1 (1.0)
Grade 5 or Death	0	0	0
Any drug-related TEAE	16 (16.5) 20	17 (18.1) 17	26 (26.0) 37
Any SAE	1 (1.0) 1	1 (1.1) 1	2 (2.0) 2
Any drug-related SAE	1 (1.0) 1	0	1 (1.0) 1
Any TEAE of special interest	1 (1.0) 1	1 (1.1) 1	2 (2.0) 2
Any TEAE leading to death	0	0	0
Any drug-related TEAE leading to death	0	0	0
Any TEAE leading to study drug discontinuation	4 (4.1) 4	3 (3.2) 3	7 (7.0) 7
Any drug-related TEAE leading to study drug discontinuation	3 (3.1) 3	0	3 (3.0) 3
Any TEAE leading to study discontinuation	4 (4.1) 4	3 (3.2) 3	7 (7.0) 7
Any drug-related TEAE leading to study discontinuation	3 (3.1) 3	0	3 (3.0) 3
Any injection site reaction	7 (7.2) 16	4 (4.3) 4	10 (10.0) 20

Source: refer to CSR FKS456-003, Table 14.3.1.1

[a] The Grade 4 TEAE was an event of blood CPK increased for 1 (1.0%) subject in the AI presentation group. The TEAE was of Grade 4 severity according to CTCAE toxicity grading, because the. This AEs was graded applying CTCAE toxicity grading (blood CPK increased, CPK level >10 ULN). As the subject was asymptomatic and not requiring intervention, the investigator did not consider this TEAE as life threatening from a clinical perspective, hence did not report this TEAE as SAE. This Grade 4 TEAE also led to IMP discontinuation.

AE = adverse event, CTCAE = common terminology criteria for adverse events, N = number of subjects, SAE = serious adverse event, TEAE = treatment-emergent adverse event, SAF = safety analysis set.

Injection site reactions occurred in 7/97 patients (7.2%) in the autoinjector group and in 4/94 patients (4.3%) in the prefilled syringe group.

Pivotal study FKS456-001

24-week core treatment period

In the pivotal study up to week 24, the frequency of TEAEs was similar in the MSB11456 (65.2%) and EU-RoActemra (62.3%) groups, respectively. Also SAE were equally frequent in both arms. AESIs was slightly more frequent in the MSB11456 group, see details later in this AR, as were TEAEs leading to treatment and study discontinuation. There were two deaths, both in the EU-RoActemra arm.

Table 36. Summary of AEs of Study FKS456-001, 24-week Core Treatment Period (SAF)

TEAE category	Number of subjects (%) and number of events		
	MSB11456 (N=302)	EU-RoActemra (N=302)	Total (N=604)
Any TEAE	197 (65.2) 459	188 (62.3) 476	385 (63.7) 935
Any drug-related TEAE	91 (30.1) 204	72 (23.8) 149	163 (27.0) 353
Any SAE	28 (9.3) 34	30 (9.9) 32	58 (9.6) 66
Any drug-related SAE	3 (1.0) 3	3 (1.0) 3	6 (1.0) 6
Any TEAE ≥ Grade 3	28 (9.3) 39	33 (10.9) 40	61 (10.1) 79
Any drug-related TEAE ≥ Grade 3	11 (3.6) 14	9 (3.0) 14	20 (3.3) 28
Any TEAE ≥ Grade 4	3 (1.0) 5	4 (1.3) 4	7 (1.2) 9
Any drug-related TEAE ≥ Grade 4	2 (0.7) 2	1 (0.3) 1	3 (0.5) 3
Death	0	2 (0.7) 2	2 (0.3) 2
Drug-related death	0	0	0
AESI	87 (28.8) 130	76 (25.2) 114	163 (27.0) 244
Drug-related AESI	38 (12.6) 65	33 (10.9) 53	71 (11.8) 118
TEAE leading to treatment discontinuation	32 (10.6) 39	22 (7.3) 27	54 (8.9) 66
Drug-related TEAE leading to treatment discontinuation	17 (5.6) 18	9 (3.0) 13	26 (4.3) 31
TEAE leading to treatment interruption	62 (20.5) 91	63 (20.9) 91	125 (20.7) 182
Drug-related TEAE leading to treatment interruption	24 (7.9) 46	25 (8.3) 41	49 (8.1) 87
TEAE leading to study discontinuation	22 (7.3) 26	15 (5.0) 18	37 (6.1) 44
Drug-related TEAE leading to study discontinuation	12 (4.0) 13	5 (1.7) 7	17 (2.8) 20
Serious injection site reaction	1 (0.3) 1	2 (0.7) 4	3 (0.5) 5

Source: refer to CSR FKS456-001 Week 30, Table 14.3.2.1.1

AESI = adverse events of special interest, SAE = serious adverse event, TEAE = treatment-emergent adverse event, SAF = safety analysis set

Note: AEs are considered Adverse Events of Special Interest (AESIs) if they are one of the following: Serious infections (defined as those requiring administration of intravenous antibiotics), Hypersensitivity and anaphylaxis or Adverse events leading to the interruption of study treatment, permanent discontinuation of study treatment or withdrawal from the study.

Injection site reactions are included in this summary only if they are considered serious or of special interest

During the Core Treatment Period of Study FKS456-001, the most commonly affected SOCs were, in descending order of frequency, investigations (21.2% subjects in the MSB11456 group and 24.8% in the EU-RoActemra group), infections and infestations (18.5% and 17.9% patients, respectively) and blood and lymphatic system disorders (13.9% and 12.6% patients, respectively).

Overall study period (up to week 63)

Updated safety data submitted in response to day 120 LoQ is shown below.

Table 37.Overall summary of treatment-emergent adverse events – overall period (Safety Analysis Set)

Adverse Event Category [n (%) m] rate per patient-year (95% CI)	MSB11456 (N=302)	EU-RoActemra/MSB11456 (N=139)	EU-RoActemra (N=163)	Total (N=604)
Any TEAE	237 (78.5) 739 2.2 (2.0 - 2.4)	105 (75.5) 342 2.0 (1.8 - 2.3)	125 (76.7) 399 2.3 (2.0 - 2.5)	467 (77.3) 1480 2.2 (2.1 - 2.3)
Any Related TEAE	106 (35.1) 297 0.9 (0.8 - 1.0)	43 (30.9) 99 0.6 (0.5 - 0.7)	46 (28.2) 108 0.6 (0.5 - 0.7)	195 (32.3) 504 0.7 (0.7 - 0.8)
Any Serious TEAE	51 (16.9) 58 0.2 (0.1 - 0.2)	20 (14.4) 26 0.2 (0.1 - 0.2)	33 (20.2) 39 0.2 (0.2 - 0.3)	104 (17.2) 123 0.2 (0.2 - 0.2)
Any Related Serious TEAE	5 (1.7) 5 0.0 (0.0 - 0.0)	1 (0.7) 1 0.0 (0.0 - 0.0)	3 (1.8) 6 0.0 (0.0 - 0.1)	9 (1.5) 12 0.0 (0.0 - 0.0)
Any Related TEAE Leading to Interruption of IMP	30 (9.9) 62 0.2 (0.1 - 0.2)	16 (11.5) 28 0.2 (0.1 - 0.2)	13 (8.0) 23 0.1 (0.1 - 0.2)	59 (9.8) 113 0.2 (0.1 - 0.2)
Any TEAE Leading to Discontinuation of Study	27 (8.9) 31 0.1 (0.1 - 0.1)	9 (6.5) 9 0.1 (0.0 - 0.1)	19 (11.7) 25 0.1 (0.1 - 0.2)	55 (9.1) 65 0.1 (0.1 - 0.1)
Any Related TEAE Leading to Discontinuation of Study	13 (4.3) 14 0.0 (0.0 - 0.1)	5 (3.6) 5 0.0 (0.0 - 0.1)	6 (3.7) 11 0.1 (0.0 - 0.1)	24 (4.0) 30 0.0 (0.0 - 0.1)
Any TEAE with Outcome of Death	0	1 (0.7) 1 0.0 (0.0 - 0.0)	3 (1.8) 3 0.0 (0.0 - 0.1)	4 (0.7) 4 0.0 (0.0 - 0.0)
Any Related TEAE with Outcome of Death	0	0	0	0
Any Serious Injection Site Reaction	2 (0.7) 5 0.0 (0.0 - 0.0)	1 (0.7) 1 0.0 (0.0 - 0.0)	2 (1.2) 4 0.0 (0.0 - 0.1)	5 (0.8) 10 0.0 (0.0 - 0.0)

CI = confidence interval, EU-RoActemra = European Union–approved RoActemra, IMP = investigational medicinal product, m = number of events, n = number of patients, SE = standard error, TEAE = treatment-emergent adverse event
Incidence per patient-year was calculated by dividing the number of events multiplied by 365.25 by the sum of the days on study for all patients.
Note: For each category, patients were included only once, even if they experienced multiple events within the category. Treatment emergence was defined as occurring or worsening (in severity or relationship to IMP) with an onset at the time of or following first treatment.
Adverse events were considered adverse events of special Interest (AESIs) if they were one of the following: serious infections (defined as those requiring administration of intravenous antibiotics), hypersensitivity and anaphylaxis, or adverse events leading to the interruption of IMP, permanent discontinuation of IMP, or withdrawal from the study.
Injection site reactions were included in this summary only if they were considered serious or of special interest.
Note: The 95% CI was calculated as: LnRate= log(Rate), and SE of LNRate=1/sqrt(x); 95% CI Rate = exp(LnRate +/- 1.96*SE).
Source: Listing 16.2.7.1, Dataset: ADAESUM, Program: t-overallae-overall.sas, Output: T-14-03-02-01-03-overallae-overall.rtf, Generated on: 2022-10-07T01:17

Injection site reactions

During the 24-week Core Treatment Period, the proportion of patients with at least 1 ISR was 11.3% in the MSB11456 and 4.6% in the EU-RoActemra groups, respectively.

Table 38. Injection site reactions in Study FKS456-001, 24-week core treatment period (SAF)

Injection site reaction	Number of subjects (%) and number of events		
	MSB11456 (N=302)	EU-RoActemra (N=302)	Total (N=604)
Any injection site reaction	34 (11.3) 402	14 (4.6) 50	48 (7.9) 452
Bruising	2 (0.7) 2	0	2 (0.3) 2
Erythema	28 (9.3) 137	9 (3.0) 18	37 (6.1) 155
Hematoma	2 (0.7) 5	1 (0.3) 1	3 (0.5) 6
Infection	2 (0.7) 4	0	2 (0.3) 4
Pain	10 (3.3) 35	4 (1.3) 4	14 (2.3) 39
Pruritus	22 (7.3) 131	6 (2.0) 18	28 (4.6) 149
Rash	2 (0.7) 5	1 (0.3) 1	3 (0.5) 6
Swelling	9 (3.0) 81	4 (1.3) 8	13 (2.2) 89
Warming	1 (0.3) 2	0	1 (0.2) 2

Source: refer to CSR FKS456-001 Week 30, Table 14.3.6.3.1
SAF = safety analysis set.

In the Overall Period (up to week 63), the proportion of patients with at least 1 injection site reaction was 12.3% and 8.0% of patients in the MSB11456 and EU-RoActemra groups, respectively. All of

these were considered related to the investigational drug, but very few cases (1 patient in the MSB11456 arm and 2 patients in the RoActemra arm in the Core Period) resulted in study drug discontinuation.

2.6.8.3. Serious adverse event/deaths/other significant events

For a summary of the results from SC PK study MS200740-0001 and IV PK study FKS456-002, please refer to Table 33-Table 34.

Pivotal study FKS456-001

During the Core Treatment Period of Study FKS456-001, the proportion of subjects with at least 1 SAE was 9.3% in the MSB11456 group and 9.9% in the EU-RoActemra group (Table 36). The most common SAE in both treatment groups were infections.

A total of 5 deaths were reported up to Week 63:

- 1 death in an unrandomised patient during the Screening Period
- 3 deaths during the Overall Period up to Week 55 (COVID-19, acute myocardial infarction, COVID-19 pneumonia, all in the EU-RoActemra group),
- 1 death between Week 55 and Week 63 of the Overall Period (myocardial infarction in the MSB11456 to EU-RoActemra group).

2.6.8.4. Laboratory findings

Mean change from baseline to week in Hb, leukocytes, platelets and neutrophils were similar between the arms. No clinically meaningful differences in mean or median biochemistry values were noted across the treatment groups.

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 for biosimilars.

2.6.8.7. Immunological events

The bioanalytical methods and ADA results are described in section 3.3.1 Clinical pharmacology.

The immunogenicity of MSB11456 was evaluated directly in comparison to the originator product, in the three randomised, double-blind parallel group, clinical studies as described previously. In total, the ADA Evaluable population comprised 1417 subjects across the three clinical studies. A highly sensitive (limit of detection approximately 4 ng positive control antibody/mL) and drug-tolerant anti-drug antibody (ADA) assay was applied in conjunction with a cell-based neutralising antibody (NAb) assay to monitor the humoral immune response to tocilizumab.

Study MS200740-0001
In Study MS200740-0001, the detected ADA incidence was similar for healthy volunteers receiving a single 162 mg SC dose of MSB11456 (67.1%) or EU-RoActemra (65.8%), and slightly lower in subjects receiving US-Actemra (53.7%). The incidence of NAb against tocilizumab was 2.6% in the MSB11456 treatment arm, 1.3% in the US-Actemra treatment arm, and 2.7% in the EU-RoActemra treatment arm.

Study FKS456-002

The ADA incidence for healthy volunteers receiving a single IV infusion dose of 8 mg/kg of MSB11456 or US-Actemra was 91.9% and 98.5 % respectively.

Study FKS456-001

A high incidence of ADA positive results was detected in rheumatoid arthritis patients treated with MSB11456 (97% of total ADA positive patients for Week 0 to Week 30) and EU-RoActemra (95.7%) and 97.1% for patients who switched from EU-RoActemra to MSB11456 at Week 24. ADA incidence appeared to peak at Week 2 all both treatment groups (Table 39 and Figure 12).

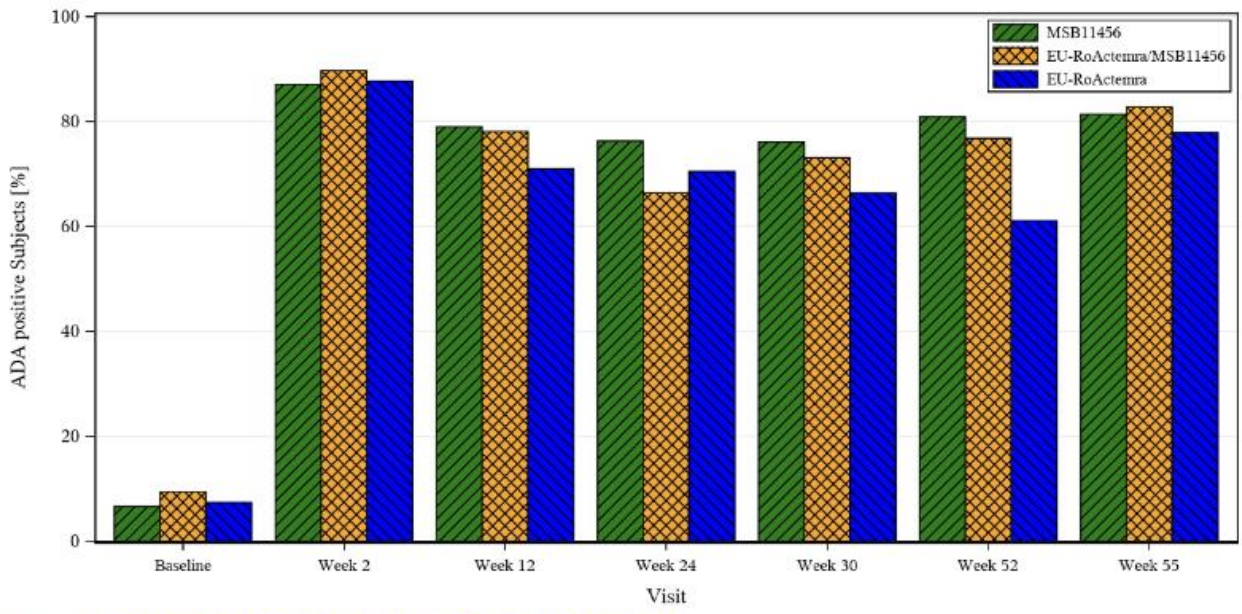
Table 39. ADA Prevalence and median ADA titre by time point for overall period (Safety Analysis Set)

Timepoint	ADA prevalence % (n/N*)			ADA titer Median		
	MSB11456 (N=302)	EU-RoActemra /MSB11456 (N=139)	EU-RoActemra (N=163)	MSB11456 (N=302)	EU-RoActemra /MSB11456 (N=139)	EU-RoActemra (N=163)
Overall	98.7 (295/299)	100 (139/139)	98.1 (159/162)	120.0	120.0	60.0
Pre-dose	6.6 (20/302)	9.4 (13/139)	7.4 (12/163)	60.0	120.0	60.0
Week 2	87.1 (250/287)	89.7 (122/136)	87.7 (136/155)	60.0	60.0	60.0
Week 12	79.0 (222/281)	78.1 (107/137)	71.0 (110/155)	120.0	120.0	120.0
Week 24	76.3 (209/274)	66.4 (91/137)	70.5 (103/146)	120.0	120.0	120.0
Week 30	76.1 (204/268)	73.1 (98/134)	66.4 (89/134)	120.0	120.0	60.0
Week 52	80.9 (199/246	76.8 (96/125)	61.1 (77/126)	240.0	120.0	60.0
Week 55	81.4 (197/242)	82.8 (101/122)	77.9 (95/122)	240.0	240.0	120.0

ADA = Anti-drug antibody; n = number of patients with positive status; N* = number of patients with a valid ADA result; N = number of subjects in the safety population; Titer = Reciprocal of total sample dilution factor, including the assay minimum required dilution; Overall Titer = maximal value determined across all time points except Baseline (pre-dose)

Source: FKS456-001 CSR Table 14.2.8.1.3 & Listing 16.2.6.8

Figure 12 ADA prevalence – overall period in Study FKS456-001 (Safety Analysis Set)



Source: FKS456-001 CSR Table 14.2.8.1.3 & Figure 14.3.1.1.2

ADA titres and Nab incidence up to week 55 is shown below.

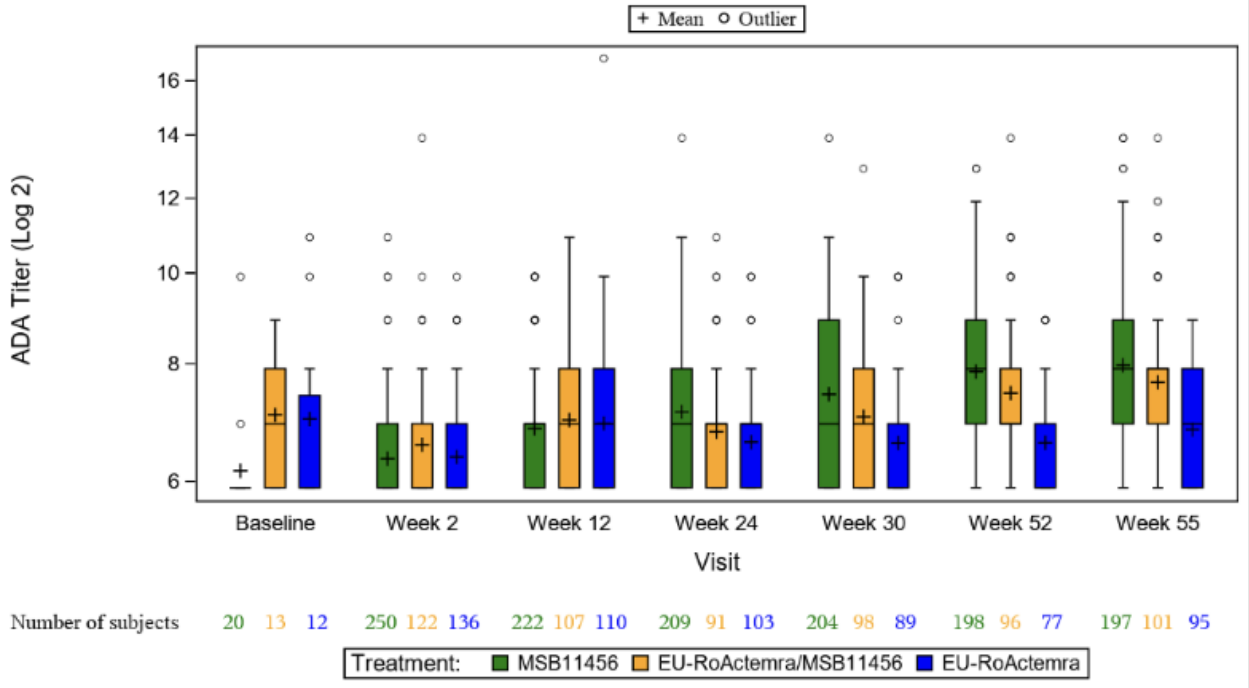
Table 40. Geometric mean ADA titre and NAb prevalence by time point for overall period (Safety Analysis Set)

Timepoint	ADA titer Geometric mean (min, max)			NAb prevalence % (n/N*)		
	MSB11456 (N=302)	EU-RoActemra /MSB11456 (N=139)	EU-RoActemra (N=163)	MSB11456 (N=302)	EU-RoActemra /MSB11456 (N=139)	EU-RoActemra (N=163)
Overall	147.5 (60,15360)	133.0 (60,15360)	101.3 (60,122880)	19.1 (57/299)	29.5 (41/139)	19.1 (31/162)
Pre-dose	71.4 (60,960)	133.5 (60,480)	127.1 (60,1920)	0	0	0
Week 2	81.2 (60,1920)	94.5 (60,15360)	82.7 (60,960)	3.8 (11/287)	3.7 (5/136)	3.2 (5/155)
Week 12	113.8 (60,960)	125.6 (60,1920)	120.8 (60,122880)	2.5 (7/281)	4.4 (6/137)	3.2 (5/155)
Week 24	138.4 (60,15360)	109.5 (60,1920)	97.4 (60,960)	2.9 (8/274)	4.4 (6/137)	5.5 (8/146)
Week 30	172.0 (60,15360)	130.6 (60,7680)	96.5 (60,960)	6.0 (16/268)	9.7 (13/134)	3.0 (4/134)
Week 52	230.9 (60,7680)	174.7 (60,15360)	96.7 (60,480)	1.6 (4/246)	2.4 (3/125)	1.6 (2/126)
Week 55	251.2 (60,15360)	200.8 (60,15360)	112.4 (60,480)	7.0 (17/242)	6.6 (8/122)	9.0 (11/122)

ADA = Anti-drug antibody; n = number of patients with positive status; N* = number of patients with a valid ADA result; NAb = Neutralizing antibody; N = number of subjects in the safety population; Titer = Reciprocal of total sample dilution factor, including the assay minimum required dilution; Overall Titer = maximal value determined across all time points except Baseline (pre-dose)

Source: FKS456-001 CSR Table 14.2.8.1.3 & Listing 16.2.6.8

Figure 13 Antidrug antibody titre – box plot – overall period (Safety Analysis Set)



Source: CSR FKS456-001

Impact of ADA on safety

The following were considered predefined adverse events of special interest (AESI) potentially related to immunogenicity for this study:

- Serious infections (defined as those requiring administration of intravenous antibiotics)
- Hypersensitivity and anaphylaxis
- Adverse events leading to the interruption of study treatment, permanent discontinuation of study treatment or withdrawal from the study.

The incidence of any AESI potentially related to immunogenicity for the ADA positive subpopulations in each treatment group (Overall Period) was 37.6% for MSB11456, 34.5% for EU-RoActemra and 35.8% for patients who switched treatment from EU-RoActemra to MSB11456 at Week 24 (Table 41).

Table 41. Treatment-emergent adverse events of special interest by ADA status – overall period (Safety Analysis Set)

System Organ Class /Preferred Term [n (%) m]	ADA Status	MSB11456 (N=302)	EU-RoActemra/ MSB11456 (N=139)	EU-RoActemra (N=163)	Total (N=604)
Subgroups, n1	Positive	295	139	159	593
	Negative	7	0	4	11
Any Treatment-Emergent AESI	Positive	111 (37.6) 184	48 (34.5) 80	57 (35.8) 94	216 (36.4) 358
	Negative	4 (57.1) 8	0	1 (25.0) 1	5 (45.5) 9

n = Number of patients; m = Number of events

n1 = The denominator of the percentages is based on n1 (number of subjects in each subgroup).

Note: Adverse events were coded using MedDRA version 23.1. For each system organ class and preferred term, patients are included only once, at the ADA status.

Treatment-emergence is defined as occurring or worsening (in severity or relationship to study drug) with an onset at the time of or following first treatment.

AEs are considered Adverse Events of Special Interest (AESIs) if they are one of the following: Serious infections (defined as those requiring administration of intravenous antibiotics), Hypersensitivity and anaphylaxis or Adverse events leading to the interruption of study treatment, permanent discontinuation of study treatment or withdrawal from the study.

Source: FKS456-001 CSR Listing 16.2.7.2

The incidence of hypersensitivity events for the ADA positive subpopulations in each treatment group (Overall Period of 52 weeks) was 5.4% for MSB11456, 8.2% for EU-RoActemra and 10.8% for patients who switched treatment at Week 24 from EU-RoActemra to MSB11456.

There were no anaphylactic reactions reported.

There was a higher incidence of injection site reactions for the ADA positive sub-population in the MSB11456 treatment group (12.2%) compared to the EU-RoActemra group (8.2%). It should be noted that almost all patients in both arms were ADA-positive (98.7% vs 98.1%, respectively for MSB11456 and RoActemra).

Table 42. Injection site reactions by ADA status – overall period in Study FKS456-001 (Safety Analysis Set)

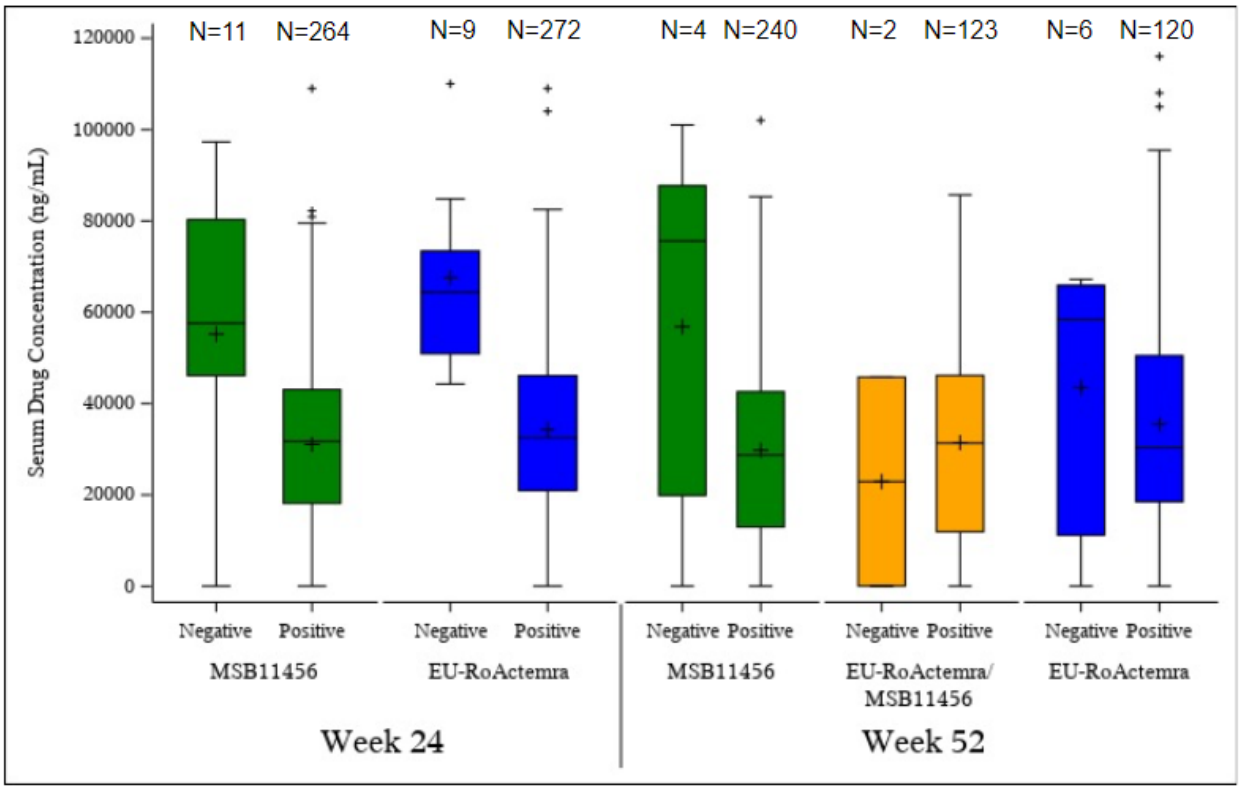
Injection Site Reaction [n (%) m, e]	MSB11456 (N=302)	EU-RoActemra/ MSB11456 (N=139)	EU-RoActemra (N=163)	Total (N=604)
ADA Positive Subjects	295	139	159	593
One or more ISR Yes	36 36 (12.2) 583, 0.044	9 9 (6.5) 158, 0.024	13 13 (8.2) 28, 0.004	58 58 (9.8) 769, 0.029

ISR = Injection Site Reaction; m = mentions; e = normalized event rate defined as the number of events divided by the number of injections received.
Denominator for the percentage of 'one or more ISR' is based on number of subjects in respective subgroups.
Source: FKS456-001 CSR Listing 16.2.13.1 & Table 14.2.8.1.3

Impact of ADA status on drug levels and efficacy

The distribution of serum drug trough levels by ADA status is shown in Figure 14.

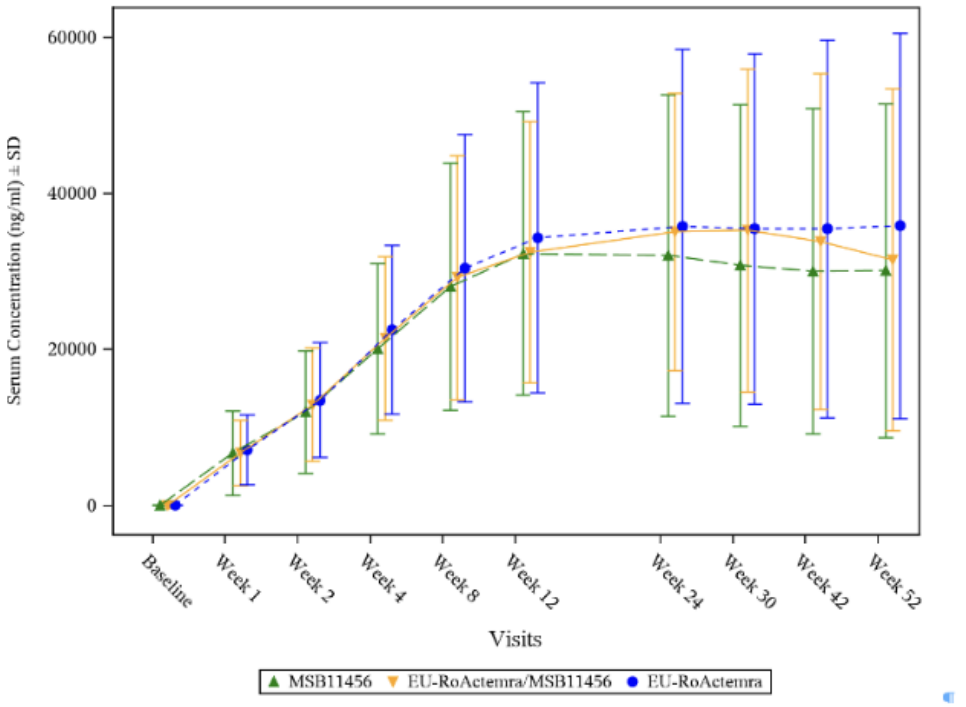
Figure 14 Boxplot of serum drug concentration at Week 24 and at Week 52 by ADA status - Core and Extended Period (Safety Analysis Set)



ADA overall status and Serum Drug Concentration data at Week 24 refer to Core period, and data at Week 52 refer to Extended Period. The boxes are composed of Q1, median, and Q3, with the mean value indicated by the + symbol. The bars extending from the box indicate the range of values that are outside of Interquartile Range (IQR) but within 1.5*IQR. Symbols indicate individual data points that are more than 1.5*IQR from the box.
Source: FKS456-001 CSR Table 14.2.8.4.1, Table 14.2.8.4.2, Listing 16.2.6.7

A small difference in mean trough concentration is observed between the MSB11456 and EU-RoActemra arms from week 12 and onwards, and a decreased concentration is observed among patients who switch from EU-RoActemra to MSB11456 (at week 24) from week 30 and onwards (Figure 15).

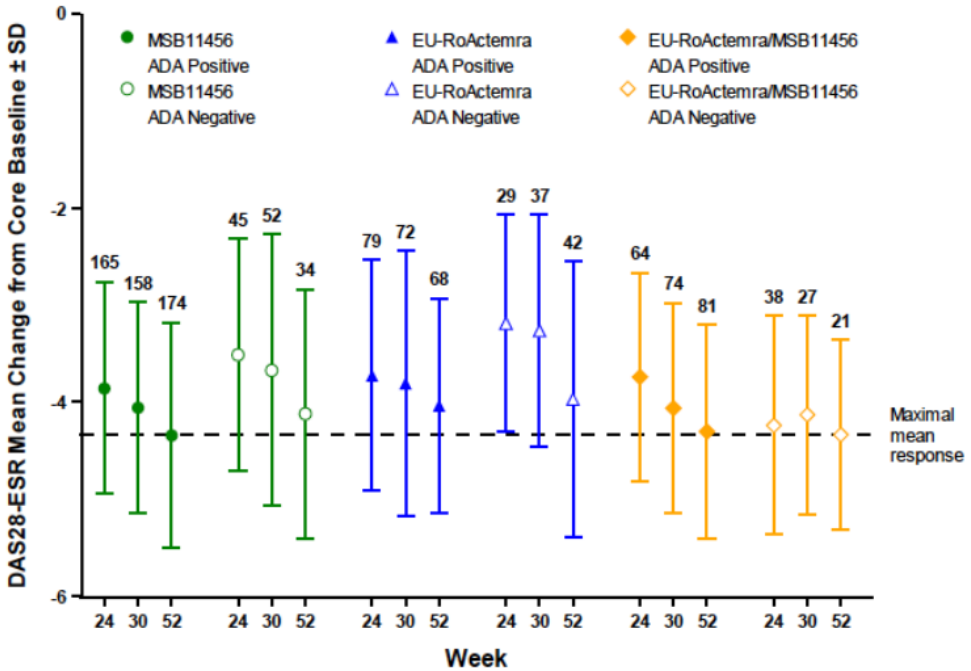
Figure 15 Mean trough drug concentration over time (Linear Scale – Overall Period (PK analysis set)



Source: Refer to CSR, Figure 9 and Figure 14.3.2.1.1

Comparison of the mean DAS28-ESR change from baseline at Week 24 (primary efficacy endpoint) and at Weeks 30 and 52 by ADA status is shown below.

Figure 16 FKS456-001 - DAS28-ESR Mean (± Std Dev) change from core baseline by ADA status at Weeks 24, 30 & 52 (Per Protocol Analysis Set, Overall Period)



ADA = Antidrug antibody. SD = Standard Deviation

Note: ADA status is the ADA status at the specific visit. Patients without ADA results are excluded from the summaries.

Source: Listing 16.2.6.1 and 16.2.6.8

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

Please refer to Table 36. In the pivotal study up to week 24, TEAEs leading to treatment discontinuation was reported in 32/302 patients (10.6%) in the MSB11456 group and in 22/302 patients (7.3%) in the EU-RoActemra group.

2.6.8.10. Post marketing experience

MSB11456 is currently not marketed in any country.

2.6.9. Discussion on clinical safety

MSB11456 is proposed as a biosimilar to RoActemra in both approved formulations (IV and SC). The most common adverse reactions noted in clinical studies with RoActemra were upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased alanine aminotransferase (ALT) and injection site reactions (ISRs) after SC administration.

In terms of immunogenicity, the detected incidence of antidrug antibodies (ADAs) was relatively low (less than 2%) in the different approved indications when RoActemra was administered as a monotherapy or in combination with methotrexate in historical studies.

The main data supporting biosimilarity from a clinical perspective originates from the comparative pivotal safety and efficacy Study FKS456-001 including 604 subjects with rheumatoid arthritis randomised to either SC MSB11456 or SC EU-RoActemra in prefilled syringe. Study FKS456-001 consists of a screening period, a double-blind 24-week core treatment period followed by an additional 28-week double-blind extended treatment period and a 12-week safety evaluation period. The original submission covered efficacy, safety, immunogenicity and PK results up to week 30 covering both the 24-week core treatment period and the first 6 weeks of the extended treatment period. In response to day 120 LoQ, the applicant submitted a new CSR including data up to Week 63, including immunogenicity data up to the latest timepoint for ADA analysis (week 55).

Supportive data are received from:

- SC PK/PD study MS200740-0001 comparing the PK, safety, and immunogenicity of MSB11456 with US-Actemra and EU-RoActemra in healthy subjects, who received a single dose of 162 mg of the assigned study medication
- IV PK study FKS456-002 comparing the PK, safety, and immunogenicity of IV administered MSB11456 with that of IV administered US-Actemra in healthy subjects, who received a single dose of 8 mg/kg of the assigned study medication
- Prefilled syringe vs autoinjector study FKS456-003 comparing the PK and safety of MSB11456 administered via PFS and AI in healthy subjects, who received SC a single dose of 162 mg MSB11456 via PFS and AI each, in the assigned treatment sequence (ie, PFS followed by AI or AI followed by PFS).

If not otherwise stated, the data presented in the safety section comes from the pivotal efficacy and safety study FKS456-001.

Exposure

During the clinical development of MSB11456, a total of 834 subjects received at least one dose of MSB11456. Of those, the study drug was administered by SC injection in 772 subjects including

139 patients who have been switched from EU-RoActemra to MSB11456, and by IV infusion in 62 subjects.

Overview of adverse events

In PK study MS200740-0001, the pattern of AEs was similar in the MSB11456 and EU-RoActemra groups, respectively. Serious AEs was more frequent in the MSB11456 group. Overall, five (5) subjects reported SAEs: 3 subjects in the MSB11456 group (appendicitis perforated Grade 3, considered related to study treatment; pneumothorax spontaneous Grade 3, considered unrelated to study treatment; abortion spontaneous Grade 1, considered related to study treatment), 1 subject in the US-Actemra group (abdominal pain Grade 3, considered related to study treatment) and 1 subject in the EU-RoActemra group (appendicitis perforated Grade 3, considered related to study treatment). Although this imbalance evokes some concern, it is likely a random finding given the few overall events. The most frequently observed TEAEs were upper respiratory tract infection, headache, oropharyngeal pain, vessel puncture site bruise and nausea. Injection site reactions were slightly more frequent in the MSB11456 group (18/231 patients, 7.8%) than in the EU-RoActemra group (12/225 patients, 5.3%). Injection site erythema and injection site bruising were reported in all treatment arms (5.3% for EU RoActemra and 6.5 % for MSB11456, 2.7% for EU RoActemra and 6.9% for MSB11456 respectively). However, less injection site reactions have been observed for US licensed Actemra. The apparent imbalance in injection site reactions has been attributed to injection site technique by the applicant and findings were considered of no clinical relevance as all these injection site reactions were mild, short duration and resolved spontaneously.

The injection site reactions observed in study MS200740-0001 must be interpreted together with the data from the pivotal study, see later in this report.

IV PK study FKS456-002 did not include any comparison against EU-RoActemra and the study is therefore of limited relevance for this assessment.

In prefilled syringe vs autoinjector study FKS456-003, it is agreed that no specific differences in safety outcomes were observed between the autoinjector and the prefilled syringe, apart from a higher occurrence of injection site reactions for the autoinjector. According to the applicant, the slightly higher frequency of ISRs observed for the AI may be due to more direct contact of the AI with the skin compared to the PFS (the AI is pushed to the skin during administration). This seems reasonable.

In the pivotal study FKS456-001 up to week 24, the frequency of TEAEs was similar in the MSB11456 (65.2%) and EU-RoActemra (62.3%) groups, respectively. Also, SAE were equally frequent in both arms. AESI was slightly more frequent in the MSB11456 group, se details later in this AR, as were TEAEs leading to treatment and study discontinuation. There were four deaths reported during the overall study, 3 in the EU-RoActemra arm (COVID-19, acute myocardial infarction, COVID-19 pneumonia) and 1 in the MSB11456 to EU-RoActemra arm (myocardial infarction).

Common adverse events

The frequencies of common adverse events were very similar between the arms. Headache was slightly more frequent in the MSB11456 arm (5%) than in the EU-RoActemra arm (2%), however this pattern was not consistent across the other studies (for example in study MS200740-0001 headache was more frequent in the EU-RoActemra arm).

Serious adverse events and deaths

Serious adverse events occurred with a similar frequency in both treatment groups. Although serious infections and musculoskeletal and connective tissue disorders were numerically higher in the biosimilar arm, this might be a random finding given the few events.

Adverse events of special interest

Overall, AESIs were numerically more frequent in the biosimilar arm. These include for example infections (12.6 vs 9.6%) and leukopenia (1.7 vs 1.0%). However, the difference between the arms is considered too small to draw any conclusions on clinically meaningful differences. No particular differences in the occurrence of hypersensitivity reactions were observed between the arms.

As previously noted in PK study MS200740-0001, injection site reactions were more frequent in the MSB11456 arm (34/302, 11.3%) than in the EU-RoActemra arm (14/302 patients, 4.6%). The main difference is observed for erythema, pain and pruritus. At day 120, the applicant was asked to further discuss this, including a justification as to why this does not constitute a meaningful difference precluding biosimilarity. In their response, the applicant argues that although a difference in prevalence of injection site reactions was observed up to week 24 (11.3% and 4.6% in the MSB11456 and RMP groups, respectively), this difference was smaller in the overall study period (12.3% and 8.0% of patients in the MSB11456 and EU-RoActemra groups, respectively). Very few cases (1 patient in the MSB11456 arm and 2 patients in the RoActemra arm) had injection site reactions that resulted in discontinuation of the study drug. The applicant considers the observed imbalance in injection site reactions to be clinically not relevant.

The applicant has discussed the potential causes for the observed numerical imbalance in injection site reactions rate. Overall, the comparison of structural, physiochemical and functional attributes using multiple batches of the proposed biosimilar product and reference product, demonstrate that MSB11456 and RoActemra show high similarity in quality attribute. This is agreed on (for details please refer to section 2.4.). There are however some possible causes for this observed difference as is further discussed below.

According to the applicant, dimerisation/aggregation reflected by high molecular weight (HMW) content might be a potential influencing factor on the occurrence of injection site reactions. However, the HMW profile of the MSB11456 clinical batches is stated to be well within the accepted quality range. Further, the amount of HMW in MSB11456 batches used in the clinical study FKS456-001 was found to be in general slightly lower than the amount of HMW observed for the EU-RMP batches used in Study FKS456-001.

Further, the applicant has discussed possible differences in composition/excipients. According to the applicant, all excipients used for the formulation of MSB11456 are well-known and widely used in the pharmaceutical industry for solutions for injection. None of the excipients used is expected to induce clinically relevant Injection site reactions or would have any other safety impact.

Finally, the applicant has discussed possible influence of immunogenicity on the injection site reactions prevalence. The proportion of ADA-positive patients with an injection site reaction was similar to the proportion of ADA-negative patients with an injection site reaction (9.8% and 9.1% of patients, respectively). The applicant concludes that due to the high incidence of ADAs it cannot be fully excluded that ADA status would have any slight influence on injection site reactions, nevertheless the likelihood is very minimal due to consistent results between MSB11456 and RoActemra irrespective of ADA status. This is agreed on.

Overall, given the well-characterised similarity between MSB11456 and EU-RoActemra from a quality and PK perspective, the observed difference in injection site reactions between the arms might be a random finding that does not indicate a true difference between MSB11456 and EU-RoActemra.

Laboratory values

Mean change from baseline to week in Hb, leukocytes, platelets and neutrophils were similar between the arms). Further, the frequencies of haematology-related adverse events (anaemia, leukopenia and thrombocytopenia) were similar in both treatment groups.

It is agreed with the applicant that no clinically meaningful differences in mean or median biochemistry values were noted across the treatment groups. No relevant differences were observed between the arms in urinalysis parameters.

No clinically relevant findings with respect to the clinical laboratory evaluation were observed in Study FKS456-002 or FKS456-003.

There were no clinically relevant findings with respect to vital signs and ECG recordings.

Immunogenicity

ADA levels were generally high in both treatment groups (>95%). This is far higher than what was observed in the RoActemra studies SC-II and SC-II, where ADA levels around 1% were observed (RoActemra SmPC). According to the applicant, the ADA sensitivity was in line with the current standards. The analytical methods are further discussed in the clinical pharmacology section.

A higher proportion of patients in the EU-RoActemra group was ADA positive at baseline (6.6% in MSB11456 group and 8.3% in EU-Roactemra group), whereas a shift is observed at week 12 and onwards with a higher proportion of ADA-positive patients in the MSB11456 than in the EU-RoActemra group (80.9% vs 61.1% [difference 19.8% in favour of RoActemra] at week 52). The similar observation is made with regards to ADA titres, with lower levels at baseline for MSB11456 than for EU-RoActemra, but higher levels for MSB11456 than for EU-RoActemra at week 30 and 52.

Among ADA-positive patients, injection site reactions occurred more frequently in the MSB11456 group (12.2%) than in the EU-RoActemra group (8.2%). There was no notable difference between ADA-positive and ADA-negative patients, however the limited number of ADA-negative patients hampers firm conclusions to be drawn.

Somewhat reassuring, no meaningful difference in ADA levels was observed in the PK studies. In SC PK study MS200740-0001, the detected ADA incidence was similar for healthy volunteers receiving a single 162 mg SC dose of MSB11456 (67.1%) or EU-RoActemra (65.8%). In the IV PK study, the ADA incidence was 91.9% for MSB11456 and 98.5 % for US-Actemra, respectively.

A difference is noted in serum drug concentration, which might be a result of an imbalance in ADAs. For details, please refer to section2.6.2..

Subgroup analyses of the primary and key secondary estimands were additionally planned by ADA and NAb status. However, these analyses were different to interpret since at least 1 subgroup category included fewer than 10% of patients in the respective analysis population and results would not have been interpretable (please refer to efficacy section).

To summarise, the observed difference in ADA prevalence between the products observed from week 12 to week 52 confers some uncertainty regarding a potential difference in immunogenicity between the products. However, it is acknowledged that the method for ADA detection is very sensitive and that the relative difference between the arms is small. Although a decrease in serum drug concentration is observed from week 12 and onwards in the MSB11456 arm compared to the EU-RoActemra arm, there are no indications that this would confer an impaired efficacy for the biosimilar. It is further acknowledged that the immunogenicity for tocilizumab in previous studies has been shown to be very low, and therefore this small potential difference is not expected to pose clinical issue and is likely due to a more sensitive method for ADA detection.

Extrapolation to other indications

According to the applicant, data support a consistent immunogenicity profile of tocilizumab across all approved indications, populations, routes and modes of administration, and regardless if the drug was used as monotherapy or in combination with csDMARDs. Therefore, the applicant considers it justified to anticipate that MSB11456 does exert a similar immunogenicity profile as the reference product in those indications and populations approved for (Ro)Actemra which were not studied in the MSB11456 clinical programme. Further, the applicant states that the safety profile of (Ro)Actemra across all approved indications and routes of administration is similar and undifferentiated with the exception of injection site reactions which occurred more frequently following the SC route than the IV route of administration. This is agreed on.

2.6.10. Conclusions on the clinical safety

To conclude, some uncertainties regarding the biosimilarity between MSB11456 and EU-RoActemra were identified during the assessment. The most important difference was a small difference in ADA prevalence between MSB11456 and EU-RoActemra.

However, there are no differences observed from a quality perspective to explain such a potential difference between the products (please refer to section 3.1 and 3.3). Taking the totality of data and the similarity observed in the quality and PK characterisation of the products into account, the small observed difference in immunogenicity does not preclude biosimilarity.

2.7. Risk Management Plan

The Safety Specification (Part II, SI-SVIII) from RMP version 0.1, dated 26-04-22 is detailed below.

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risk: **Serious infections***	**Routine risk minimization measures:** SmPC (IV and SC administration): • Section 4.3 Contraindications Active, severe infections (see Section 4.4) • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects Patient Information leaflet • Section 2 Warnings and precautions • Section 4 Possible side effects **Other risk minimization measures** • Pack size: None • Legal status: prescription only medicine **Additional risk minimization measures:** • Patient Alert Card • Patient Brochure • Healthcare Provider Brochure • Dosing Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risk: **Complications of Diverticulitis***	**Routine risk minimization measures:** SmPC: • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects Patient Information leaflet • Section 2 Warnings and precautions. • Section 4 Possible side effects **Other risk minimization measures** • Pack size: None • Legal status: prescription only medicine **Additional risk minimization measures:** • Patient Alert Card • Patient Brochure • Healthcare Provider Brochure • Dosing Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Important potential risk: **Neutropenia**	**Routine risk minimization measures:** SmPC: • Section 4.2 Posology and method of administration • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects/Laboratory evaluations Patient Information leaflet • Section 2 Warnings and precautions. • Section 4 Possible side effects **Other risk minimization measures** • Pack size: None • Legal status: prescription only medicine **Additional risk minimization measures:** • Patient Brochure • Healthcare Provider Brochure • Dosing Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Important identified risk: **Hepatoxicity**	**Routine risk minimization measures:** SmPC: • Section 4.2 Posology and method of administration (IV administration)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects Patient Information Leaflet (IV/SC administration) • Section 2 Warnings and precautions. • Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk**: In patients with RA, GCA, pJIA, sJIA, ALT and AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. **Other risk minimization measures** • Pack size: None • Legal status: prescription only medicine **Additional risk minimization measures:** • Patient Brochure • Healthcare Provider Brochure • Patient Alert Card	• None **Additional pharmacovigilance activities:** • None
Important potential risk: **Thrombocytopenia and the potential risk of bleeding**	**Routine risk minimization measures:** SmPC: • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects • Section 4.2 Posology and method of administration (IV administration) Patient Information leaflet • None **Other risk minimization measures** • Pack size: None • Legal status: prescription only medicine **Additional risk minimization measures:** • Patient Brochure • Healthcare Provider Brochure	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important potential risk: **Elevated Lipid Levels and Potential Risk of Cardiovascular /Cerebrovascular Events**	**Routine risk minimization measures:** SmPC: • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects Patient Information leaflet • Section 2 Warnings and precautions. • Section 4 Possible side effects **Other risk minimization measures** • Pack size: None • Legal status: prescription only medicine **Additional risk minimization measures:** • Patient Brochure • Healthcare Provider Brochure • Dosing Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Important potential risk: **Malignancies**	**Routine risk minimization measures:** SmPC: • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects Patient Information leaflet • None **Other risk minimization measures** • Pack size: None • Legal status: prescription only medicine **Additional risk minimization measures:** • Patient Brochure • Healthcare Provider Brochure • Dosing Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Important potential risk: **Demyelinating Disorders**	**Routine risk minimization measures:** SmPC: • Section 4.4 Special warnings and precautions for use Patient Information leaflet • None **Other risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Pack size: None • Legal status: prescription only medicine **Additional risk minimization measures:** • Healthcare Provider Brochure	
Important potential risk: **Immunogenicity**	**Routine risk minimization measures:** SmPC: • Section 4.8 Undesirable effects Patient Information leaflet • None **Other risk minimization measures** • Pack size: None • Legal status: prescription only medicine **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

2.7.1. Conclusion

The CHMP considers that the risk management plan version 0.1 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

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

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tyenne (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

The applicant is seeking approval for both administration routes and all indications for the reference medicinal product EU-RoActemra, namely:

1. Rheumatoid arthritis (RA)
2. Systemic juvenile idiopathic arthritis (sJIA) in patients 1 year (SC route) / 2 years (IV route) of age and older
3. Juvenile idiopathic polyarthritis (pJIA) in patients 2 years of age and older
4. Giant cell arteritis (GCA)
5. Chimeric antigen receptor (CAR)-T cell-induced severe or life-threatening CRS in adults and pediatric patients 2 years of age and older
6. Coronavirus disease 2019 (COVID-19) in hospitalised adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation

Use of MSB11456 in the treatment of RA, pJIA, and sJIA is proposed for both the IV and SC routes of administration, whereas treatment of GCA is through the SC route and treatment of CRS and COVID-19 disease is through the IV route only.

According to the applicant, the development of MSB11456 followed the standard stepwise approach for establishing similarity across structural and functional quality attributes, and (nonclinical and) clinical data consistent with relevant guidance advice were obtained.

The objective of the clinical development programme for MSB11456 was to evaluate the clinical similarity between MSB11456 and the reference product (Ro)Actemra, in terms of clinical pharmacology, efficacy, safety, tolerability and immunogenicity.

The clinical development programme consisted of three phase 1 studies and one phase 3 study. The phase 1 studies included healthy individuals with the objective to evaluate pharmacokinetic (PK) similarity of intravenous administration of MSB11456 versus US-Actemra (FKS456-002) and for subcutaneous administration of MSB11456 versus EU-RoActemra/US-Actemra (MS200740-0001). A third study (FK456-003) likewise included healthy participants with the aim to evaluate PK equivalence in pre-filled versus auto-injector administration of MSB114556. All phase 1 studies are finalised. The pivotal study FKS456-001 was a 1:1 randomised, double-blind, two arm study to evaluate the efficacy, safety and immunogenicity of MSB11456 compared to EU-RoActemra in patients with moderately to severely active RA (APTURA I study). The study included 604 patients randomised to either MSB11456 or EU-RoActemra SC.

The applicant has reviewed scientific advice and have broadly implemented CHMP scientific advice in their programme.

Quality

The applicant has performed an extensive biosimilarity exercise, evaluating relevant quality attributes by a panel of state-of-the-art analytical methods. The overall approach to assess analytical similarity is found acceptable.

The batches included in the biosimilarity study are found acceptable, both with respect to MSB11456 FP-IV (vial) and FP-SC (PFS), the EU approved RoActemra (RMP) and US approved Actemra (RP). The analytical similarity assessment has been performed with a combination of methods assessing the primary and higher order structures, post-translational modifications, purity and impurities and product variants. In addition, biological activities related to Fab binding, intracellular signalling activity, Fc binding and Fc effector function have been evaluated. A comparative forced degradation stability study is also presented.

Overall, the provided data indicates a high degree of similarity between MSB11456 FP-IV (vial) and FP-SC (PFS) and EU approved RoActemra. Some minor differences are noted. The applicant justifies the differences and provides arguments related to tocilizumab mode of action, results from biological characterisation, information in the literature as well as results obtained in non-clinical and clinical studies, implying that these differences are not clinically meaningful. EU-approved RoActemra and US-licensed Actemra are also considered comparable.

3.2. Results supporting biosimilarity

Quality

The applicant has performed an extensive biosimilarity exercise, evaluating relevant quality attributes by a panel of state-of-the-art analytical methods. The overall approach to assess analytical similarity is found acceptable.

Overall, the provided data indicates a high degree of similarity between MSB11456 FP-IV (vial) and FP-SC (PFS) and EU approved RoActemra. Some minor differences are noted. The applicant justifies the differences and provides arguments related to tocilizumab mode of action, results from biological characterisation, information in the literature as well as results obtained in non-clinical and clinical studies, implying that these differences are not clinically meaningful.

Pharmacokinetics

The pivotal data for demonstrating PK similarity with the reference product are obtained from two single-dose studies in healthy volunteers: Study MS200740-0001 (single-dose 162 mg SC injection) and Study FKS456-002 (single-dose 8 mg/kg IV infusion).

Study MS200740-0001 (single-dose SC injection): For all primary PK parameters ($AUC_{0-\infty}$, AUC_{0-t}, and C_{max}) and all pairwise treatment comparisons (MSB11456 versus US-Actemra; MSB11456 versus EU-RoActemra; and US-Actemra versus EU-RoActemra), the 90% CIs for the geometric LS mean ratio were contained within the predefined 80.00% to 125.00% similarity margin. Furthermore, the comparability was established also for PD parameters sIL-6R and CRP.

Study FKS456-002 (single-dose IV infusion): The statistical analysis of the biosimilarity of MSB11456 versus US-Actemra included the primary PK endpoint (AUC_{0-last}) and secondary PK parameters (C_{max} and AUC_{0-inf}). For AUC_{0-last} the 90% confidence interval for the ratio of the test and reference products fell within the conventional biosimilarity acceptance range of 80.00-125.00% when comparing MSB11456 to US-Actemra. PK similarity was additionally demonstrated for the secondary PK parameters AUC_{0-inf} and C_{max}. The GMRs (and 90% Cis) were 103.34 (98.53-108.37%) for AUC_{0-last}, 103.15% (97.86-108.73%) for AUC_{0-inf} and 101.48% (97.23-105.92%) for C_{max}.

Study FKS456-003 (PFS vs AI): For C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional bioequivalence acceptance range of 80.00-125.00% when comparing the AI to the PFS. The GMRs (and 90% CIs) were 99.67% (90.95-109.21%) for C_{max}, 102.88% (92.21-114.79%) for $AUC_{0\text{-}last}$, and 100.23% (92.67-108.41%) for $AUC_{0\text{-}inf}$.

Thus, PK equivalence was demonstrated between the PFS and AI presentations of MSB11456. Also, the secondary PK endpoints were comparable between PFS and AI presentations of MSB11456.

In the pivotal efficacy and safety study FKS456-001, PK trough concentration samples were collected from all study patients at scheduled visits. Similar mean trough concentrations were measured until week 12. A small difference in mean trough concentration was observed between the MSB11456 and EU-RoActemra arms from week 12 and onwards, and a decreased concentration is observed among patients who switch from EU-RoActemra to MSB11456 (at week 24) from week 30 and onwards. However, this did not impact the efficacy.

Efficacy

For a definition of the estimands, please refer to the statistical section.

For the primary endpoint/primary estimand 1.0 i.e., the absolute mean change of DAS28-ESR at 24 week was -3.53 (95% CI -3.74 to -3.32) for MSB11456 and -3.34 (95% CI -3.75 to -3.35) for EU-RoActemra. This corresponded in a LS mean difference of 0.01 (standard error 0.104) with a 95% CI of -0.19 to 0.22. The 95% CIs for the LS mean differences in change from baseline between groups fully included within the respective predefined equivalence intervals (-0.6 to 0.6). The mean change of DAS28-ESR in both treatment groups is considered high and clinically relevant. The results of the analyses of supportive Estimand 1.1 (per protocol approach) and Supportive Estimand 1.2 and 1.3 (DAS28-ESR Hypothetical Return-to-Baseline PP and ITT respectively) showed overall similar results as the main analysis. Likewise, sensitivity and subgroup analyses of the primary outcome/primary estimand supported the main results. In addition, the analyses of absolute mean change of DAS28-ESR from baseline at all assessment visits except Week 1 (i.e., at Weeks 2, 4, 8, 12, 16, 24, and 30) showed similar efficacy in the MSB11456 and EU-RoActemra group.

The proportion of patients reaching the key secondary endpoint/secondary estimand i.e., ACR20 response at week 24 was 80.75% in the MSB11456 group and 84.77 % in the EU-RoActemra group, corresponding to a difference (%) of -3.94 (95% CI -9.97 to 2.11). Thus, the 95% confidence interval fell within the pre-defined equivalence margin of +/-15%. Overall, the results of the supportive analyses of the ACR20 response rate at Week 24 (supportive Estimand 2.1 and 2.2) as well as sensitivity analyses were largely similar to that of the main analysis. In addition, data submitted in the second round evaluating efficacy also after 24 weeks (i.e., from baseline up until 52 weeks) showed substantially similar results as the 24-week data.

Safety

In the pivotal study FKS456-001 up to week 24, the frequency of TEAEs was similar in the MSB11456 (65.2%) and EU-RoActemra (62.3%) groups, respectively. Also, SAE were equally frequent in both arms (9.3% for MSB11456 vs 9.9% for EU-RoActemra).

The frequencies of common adverse events were similar between the arms. During the Core Treatment Period of Study FKS456-001, the most commonly affected SOCs were investigations/laboratory derangements (21.2% subjects in the MSB11456 group and 24.8% in the EU-RoActemra group), infections and infestations (18.5% and 17.9% patients, respectively) and blood and lymphatic system disorders (13.9% and 12.6% patients, respectively).

3.3. Uncertainties and limitations about biosimilarity

Quality

The overall approach to assess analytical similarity is found acceptable. Some minor differences are noted. The applicant justifies the differences and provides arguments related to tocilizumab mode of action, results from biological characterisation, information in the literature as well as results obtained in non-clinical and clinical studies, implying that these differences are not clinically meaningful.

Pharmacokinetics

Study FKS456-001: C_{trough} is the only PK parameter in the phase 3 study. A small difference in mean trough drug concentration is observed between the MSB11456 and EU-RoActemra arms from week 12 and onwards, and a decreased concentration is also observed among patients who switch from EU-RoActemra to MSB11456 (at week 24) from week 30 and onwards. This raises some concern on a potential impact on the long-term efficacy of the biosimilar. However, no difference in efficacy between the products could be observed in the 52-week clinical study.

Efficacy

From an efficacy perspective the overall data indicate similar clinical efficacy in MSB11456 as compared to EU-RoActemra.

Safety

Injection site reactions occurred with a higher frequency in the MSB11456 arm than in the EU-RoActemra arm. In PK study MS200740-0001, injection site reactions were slightly more frequent in the MSB11456 group (18/231 patients, 7.8%) than in the EU-RoActemra group (12/225 patients, 5.3%). The same tendency was observed in the pivotal study FKS456-001, where injection site reactions were more frequent in the MSB11456 arm (34/302, 11.3%) than in the EU-RoActemra arm (14/302 patients, 4.6%) during the core 24-week period of the study. However, in the Overall Period (up to week 63), the difference was smaller with a proportion of patients with at least 1 injection site reaction of 12.3% and 8.0% of patients in the MSB11456 and EU-RoActemra groups, respectively.

Immunogenicity

ADA levels were generally high in both treatment groups (>95%). This is far higher than what was observed in the RoActemra studies SC-1I and SC-II, where ADA levels around 1% were observed (RoActemra SmPC) indicating that a very sensitive method for ADA detection has been used.

In the pivotal study FKS456-001, a higher proportion of patients in the EU-RoActemra group was ADA positive at baseline (6.6% in MSB11456 group and 8.3% in EU-Roactemra group), whereas a shift is observed at week 12 and onwards with a higher proportion of ADA-positive patients in the MSB11456 than in the EU-RoActemra group (80.9% vs 61.1% [difference 19.8% in favour of RoActemra] at week 52). Somewhat reassuring, no clinically meaningful increased ADA prevalence for the biosimilar was observed in the PK studies. In SC PK study MS200740-0001, the detected ADA incidence was similar for healthy volunteers receiving a single 162 mg SC dose of MSB11456 (67.1%) or EU-RoActemra (65.8%). In the IV PK study, the ADA incidence was 91.9% for MSB11456 and 98.5 % for US-Actemra, respectively.

3.4. Discussion on biosimilarity

From a quality perspective, an extensive biosimilarity exercise has been performed, evaluating relevant quality attributes by a panel of state-of-the-art analytical methods. The overall approach to assess analytical similarity is found acceptable.

Overall, the provided data indicates a high degree of similarity between MSB11456 FP-IV (vial) and FP-SC (PFS) and EU approved RoActemra. Some minor differences are noted. The applicant justifies the differences and provides arguments related to tocilizumab mode of action, results from biological characterisation, information in the literature as well as results obtained in non-clinical and clinical studies, implying that these differences are not clinically meaningful. EU-approved RoActemra and US-licensed Actemra are also considered comparable.

From a pharmacokinetic perspective, the available PK/PD data overall support biosimilarity versus the EU reference product RoActemra.

From an efficacy perspective the results overall show evidence of therapeutic equivalence between MSB11456 and EU-RoActemra in this sensitive clinical model of rheumatoid arthritis, and therefore, supports biosimilarity.

From a safety perspective, a small difference in ADA prevalence was observed between MSB11456 and EU-RoActemra. There are no indications that this would impair the efficacy of the biosimilar. There are no differences observed from a quality perspective to explain such a potential difference in immunogenicity. Taking the totality of data and the similarity observed in the quality and PK characterisation of the products into account, the products are considered biosimilar.

3.5. Extrapolation of safety and efficacy

Inflammatory diseases for which RoActemra is approved are associated with enhanced IL-6 production. 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.

3.6. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Tyenne 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 Tyenne is favourable in the following indication(s):

Tyenne 20 mg/mL concentrate for solution for infusion

"Tyenne, 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, Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tocilizumab 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.

Tyenne 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.

Tyenne 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. Tyenne can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Tyenne 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.

Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tyenne 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."

Tyenne 162 mg solution for injection in pre-filled syringe

"Tyenne, 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, Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tocilizumab 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.

Tyenne 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. Tyenne can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Tyenne 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.

Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

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

Tyenne 162 mg solution for injection in pre-filled pen

"Tyenne, 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, Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tocilizumab 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.

Tyenne 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). Tyenne can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Tyenne 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).

Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tyenne 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 conditions listed in annex II is in line with the conditions for the originator RoActemra.

These include the following 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 Tyenne 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 subcutaneous route of administration) (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 Tyenne may develop complications of diverticulitis which can become serious if not treated.
- to address the risk that patients using Tyenne 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.