BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	351(k) BLA
Application Number	BLA 761275
Received Date	May 30, 2022
BsUFA Goal Date	May 31, 2023
Division/Office	DRTM/OII/OND
Review Completion Date	See DARRTS stamped date
Product Code Name	MSB11456
Proposed Nonproprietary Name[1]	Tocilizumab-aazg
Proposed Proprietary Name[1]	Tyenne
Pharmacologic Class	Interleukin-6 (IL-6) receptor antagonist
Applicant	Fresenius Kabi USA, LLC.
Applicant Proposed Indication(s)	1. Rheumatoid Arthritis (RA) 2. Giant Cell Arteritis (GCA) 3. Polyarticular Juvenile Idiopathic Arthritis (PJIA age ≥ 2 years) 4. Systemic Juvenile Idiopathic Arthritis (SJIA age ≥ 2 years)
Recommendation on Regulatory Action	Complete Response

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

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OBP = Office of Biotechnology Products
OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error and Prevention Analysis
DRISK = Division of Risk Management

Glossary

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

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

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1. Executive Summary

1.1. Product Introduction

Fresenius Kabi USA, LLC. (also referred to as "Applicant" in this review) has submitted a biologics license application (BLA) under section 351 (k) of the Public Health Service Act (PHS Act) for MSB11456 as a proposed biosimilar to US-licensed Actemra (tocilizumab).

MSB11456 is a humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass produced in Chinese Hamster Ovary (CHO) cells using recombinant DNA technology and proposed as a biosimilar to U.S.-licensed Actemra. MSB11456 binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and has been shown to inhibit IL-6-mediated signaling through these receptors.

The Applicant is seeking licensure of MSB11456 for the following indications for which US-licensed Actemra is licensed[2]:

1. Rheumatoid Arthritis (RA):
    - Treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
2. Giant Cell Arteritis (GCA):
    - Treatment of adult patients with giant cell arteritis.
3. Polyarticular Juvenile Idiopathic Arthritis (PJIA):
    - Treatment of patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.
4. Systemic Juvenile Arthritis (SJIA):
    - Treatment of patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

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

Not applicable.

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

Tocilizumab is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1k (gamma 1, kappa) subclass with a

[2] FDA-approved Actemra labeling

typical H2L2 polypeptide structure. Tocilizumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and has been shown to inhibit downstream IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as RA.

MSB11456 has the same mechanism of action as that of US-licensed Actemra. In addition, the OBP product quality review team has determined that MSB11456 has the same routes of administration, dosage form, and strengths as US-licensed Actemra.

MSB11456 is proposed as below:

For intravenous (IV) infusion:

- Injection: 80 mg/4 mL single-dose vials for further dilution prior to IV infusion
- Injection: 200 mg/10 mL single-dose vials for further dilution prior to IV infusion
- Injection: 400 mg/20 mL single-dose vials for further dilution prior to IV infusion

For subcutaneous (SC) injection:

- Injection: 162 mg/0.9 mL single-dose prefilled syringe (PFS)
- Injection: 162 mg/0.9 mL single-dose prefilled autoinjector (AI)

Each strength of MSB11456 in vials, PFS, and AI is the same as that of US-Actemra. MSB11456 also has the same dosage form and route of administration as those of US-Actemra.

Additionally, the condition(s) of use for which the Applicant is seeking licensure have been previously approved for US-Actemra.

1.4. Inspection of Manufacturing Facilities

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

(b) (4) is responsible for MSB11456 drug substance manufacturing. A pre-license inspection (PLI) was conducted from (b) (4). The inspection concluded with a three-item FDA Form 483 and a facility recommendation of approve.

Fresenius Kabi Austria GmbH (FK-Graz), Austria (FEI 3003708554) is responsible for MSB11456 drug product manufacturing for the single-dose glass vial. A PLI was

conducted from March 20 to March 28, 2023. A three-item Form FDA 483 was issued, with the inspection field recommendation of withhold, pending the firm's adequate response to objectionable conditions. Refer to the FDA Form 483 for a list of the observations. The response to the FDA Form 483 observations was not adequate, and the final inspection conclusion was Official Action Indicated (OAI) and a recommendation of withhold.

(b) (4) is responsible for MSB11456 drug product manufacturing for the single-dose prefilled glass syringe/autoinjector. A PLI was conducted from (b) (4). A five-item Form FDA 483 was issued, with the inspection field recommendation of withhold, pending the firm's adequate response to objectionable conditions. Refer to the FDA Form 483 for a list of the observations. The response to the FDA Form 483 observations was not adequate, and the final inspection conclusion was OAI and a recommendation of withhold.

Based on the final inspection conclusions for Fresenius Kabi Austria GmbH (FK-Graz), Austria and (b) (4), the OPMA team recommended a Complete Response action for BLA 761275 from the facilities assessment standpoint.

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

Fresenius Kabi USA, LLC. provided adequate data to establish the scientific bridge to justify the relevance of data generated from the comparative clinical study FKS456-001, which used EU-RoActemra as the non-US-licensed comparator product, to the assessment of biosimilarity:

- The Office of Pharmaceutical Products (OPQ), CDER has determined, and I agree, that based on the data provided by the Applicant, the analytical component of the scientific bridge between MSB11456, US-Actemra, and EU-RoActemra was established.
- The Office of Clinical Pharmacology (OCP) has determined, and I agree, that based on the data provided by the Applicant, the PK data establish the PK component of the scientific bridge.

1.6. Biosimilarity Assessment

Table 1. Summary and Assessment of Biosimilarity

Comparative Analytical Studies[3]: The Office of Pharmaceutical Products, OPQ, CDER has concluded, and I agree, that:	
Summary of Evidence	• MSB11456 is highly similar to US-Actemra notwithstanding minor differences in clinically inactive components • Each strength of MSB11456 in single-dose vials, PFS, and AI is the same as that of US-Actemra • The dosage form and routes of administration are also the same as that for US-Actemra • The analytical component of the scientific bridge between MSB11456, US-Actemra, and EU-RoActemra was established to support the relevance of data generated from studies using EU-RoActemra as the comparator to the assessment of biosimilarity
Assessment of Residual Uncertainties	• There are no residual uncertainties from the product quality assessment.
Animal/Nonclinical Studies: The Pharmacology and Toxicology team concluded, and I agree, that:	
Summary of Evidence	• The information in the pharmacology/toxicology assessment supports the demonstration of biosimilarity
Assessment of Residual Uncertainties	• There are no residual uncertainties from the pharmacology/toxicology assessment
Clinical Studies	
Clinical Pharmacology Studies: **The Clinical Pharmacology team concluded, and I agree, that:**	

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

Summary of Evidence	• PK similarity has been demonstrated between MSB11456 and US-Actemra (Study MS200740-001 and Study FSK456-002), and supports a demonstration of no clinically meaningful differences between MSB11456 and US-Actemra for both IV and SC routes of administration • PK similarity between MSB11456, US-Actemra, and EU-RoActemra provides the PK component of the scientific bridge to support the relevance of the comparative data generated using EU-RoActemra to the assessment of biosimilarity • Similar incidence of anti-drug antibody (ADA) and neutralizing antibody (NAb) formation between MSB11456 and US-Actemra in healthy subjects (Study MS200740-001 and Study FSK456-002) and between MSB11456 and EU-RoActemra in subjects with RA (Study FKS456-001), including following the single transition from EU-RoActemra to MSB11456 • Given the scientific bridge was established (based on the analytical and PK comparisons) between MSB11456, US-Actemra, and EU-RoActemra to justify the relevance of data generated with EU-RoActemra as the comparator, these collective immunogenicity results support a demonstration of no clinically meaningful differences between MSB11456 and US-licensed Actemra • PK of MSB11456 administered using PFS and AI was comparable (Study FSK456-003)
Assessment of Residual Uncertainties	• There are no clinical pharmacology residual uncertainties regarding the PK assessments
Additional Clinical Studies: **The Clinical and Statistical teams concluded, and I agree, that:**	

Summary of Evidence	• In the comparative clinical study FKS456-001, there were no meaningful differences in terms of efficacy between MSB11456 and EU-RoActemra, and the frequency of treatment emergent adverse events, serious events, and events leading to discontinuation of investigational medicinal product (IMP) had no meaningful differences between the treatment arms • Given the scientific bridge established (based on the analytical and PK comparisons) between MSB11456, US-Actemra, and EU-RoActemra to justify the relevance of the data generated with EU-RoActemra as the comparator, the collective evidence from submitted clinical studies, including the comparative clinical study FKS456-001, supports a demonstration of no clinically meaningful differences between MSB11456 and US-Actemra in the studied indication (RA)
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical or statistical perspective regarding the demonstration of no clinically meaningful differences between MSB11456 and US-Actemra
Extrapolation of Data to Support Licensure as a Biosimilar	
Summary of Evidence	DRTM has determined that the Applicant has provided adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of data and information submitted, including clinical data from the studied population (RA), to support licensure of MSB11456 as a biosimilar, under section 351(k) of the PHS Act, for the following indications for which US-licensed Actemra has been previously approved: o Treatment of adult patients with giant cell arteritis o Treatment of patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis o Treatment of patients 2 years of age and older with active systemic juvenile idiopathic arthritis
Assessment of Residual Uncertainties	• There are no residual uncertainties regarding the extrapolation of data and information to support licensure of MSB11456 as a biosimilar to US-Actemra for the above indications

1.7. Conclusions on Approvability

In considering the totality of the evidence submitted, the data submitted by the Applicant show that MSB11456 is highly similar to US-Actemra, notwithstanding minor differences

in clinically inactive components, and that there are no clinically meaningful differences between MSB11456 and US-Actemra in terms of the safety, purity, and potency of the product. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that MSB11456 is biosimilar to US-Actemra for each of the following indications for which US-Actemra has been previously approved and for which the Applicant is seeking licensure of MSB11456: RA, GCA, PJIA in patients 2 years and older, and SJIA in patients 2 years and older.[4]

However, data submitted in this application is not sufficient to support a conclusion that the manufacture of MSB11456 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. Therefore, the FDA review team recommends a Complete Response for this application, and the CDTL/ Division Signatory agree with that recommendation. The Complete Response Letter will outline the deficiencies and the information and data required to address the deficiencies.

Author:
Rachel Glaser, M.D.
Cross-Discipline Team Leader (CDTL)

2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

The Division had multiple interactions with the Applicant during the development of MSB11456. Key discussions are detailed in this section.

The Biosimilar Initial Advisory (BIA) meeting on June 16, 2016 focused on the Sponsor's plan to develop both IV and SC formulations of MSB11456. The Agency advised that it may be reasonable to reference data generated from the SC program for the IV formulation if an adequate bridge could be established to rely on the data, including the comparative clinical study (CCS). The scientific justification should include information supporting the PK similarity between IV MSB11456 and IV Actemra and analytical similarity of IV MSB11456 to IV US-Actemra. In discussion of the planned 3-way PK bridging study, the Agency recommended assessment of AUC_{last} as a coprimary endpoint. With regard to the design of the proposed comparative clinical study comparing SC MSB11456 to SC EU-Ro-Actemra, the Agency recommended the primary endpoint assessment of DAS28 be moved from Week (b) (4) to Week 24, based on the submitted historical information, and provided comments on the proposed similarity

[4]The proposed MSB11456 labeling states: "Biosimilarity of TYENNE has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s), strength(s), dosage form(s), and route(s) of administration) described in its Full Prescribing Information."

margin, requesting additional statistical and clinical justification. The Agency advised that either ACR20 or DAS28 was acceptable as the primary endpoint if there are sufficient historical data to determine the similarity margin. The Agency agreed that it was reasonable to start with the weekly dosing regimen to avoid confounding due to need for dose up titration prior to the primary endpoint assessment, but the Sponsor should provide justification that the weekly dose was as sensitive as the every other week dose.

At a subsequent Biological Product Development (BPD) Type 2 meeting on March 1, 2018, the Agency indicated that the single transition period in the CCS should remain blinded and that 6-8 weeks of safety and immunogenicity data are expected at the time of an original BLA submission. In addition, the study drug administrator should be blinded to avoid potential bias. Statistical advice included discussion that the primary analysis should be performed on the intention-to-treat (ITT) set, that the similarity margin for a proposed primary endpoint of response rate for at least 20% improvement in American College of Rheumatology Core Set Measurements (ACR20 response rate) at Week 24 should be no more than ± 12% using a 95% Newcombe confidence interval, and the importance of prevention of missing data. Analytical controls required to interpret ADCC and CDC assay results were also discussed.

At a BPD Type 2 meeting on March 11, 2020, the Agency advised the Applicant to conduct separate clinical PK studies for 8 mg/kg IV and 162 mg SC formulations in order to support comparisons of the linear and non-linear portions, respectively, of the PK profile for MSB11456. Due to the non-linear PK of tocilizumab, $AUC_{0\text{-}t}$, instead of $AUC_{0\text{-}inf}$, should be used as the primary PK endpoint in the IV PK study. Guidance was also provided on the device-related analysis and design verification plan for a proposed AI. The Agency did not agree with the proposal to (b) (4) and did not agree that (b) (4) for the AI without additional justification.

In BPD Type 2 written responses, provided June 16, 2021, the Agency agreed with the proposed clinical data package and data standards, as well as the proposed main and alternative estimands for the primary and secondary endpoints and strategies and statistical methods. The Agency clarified that the initial BLA submission should also include the data from the single transition period of the CCS. The Sponsor confirmed that the original submission will include data through the single transition of the CCS at the BPD meeting on June 30, 2021.

Additionally, at the BPD Type 2 meeting on June 30, 2021, the Agency provided guidance on the device information required with the original BLA submission as well as analytical comparability approaches and similarity assessments. The Agency agreed with the Sponsor's plan to not submit a formal integrated/pooled safety data analysis and that the Summaries of Clinical Efficacy (SCE) and Clinical Safety (SCS) may replace the Integrated Summaries of Efficacy (ISE) and Safety (ISS) if appropriately detailed and with explanation placed in each affected module. The Agency also agreed

with the submission of data for both IV and SC routes of administration under a single BLA.

In pre-BLA BPD Type 4 responses, communicated March 24, 2022, the Agency agreed with the use of the date of the BLA submission as the cutoff date for the 4-month safety update report, given that the data cutoff date for the Week 30 Clinical Study Report (CSR) had already passed in October 2021. The Agency agreed with the plan to submit results from human factors (HF) studies in the BLA and provided reference to the relevant guidance on submission of HF studies to Drug and Biologic Applications, and advised where they should be placed in the submission. The Agency also agreed that the labeling concept appeared reasonable, noting that the assessment of labeling and packaging design would be review issues. Additional guidance was provided by Product Quality and CMC microbiology regarding the content and format of information for the BLA submission.

2.2. Studies Submitted by the Applicant

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

The clinical studies submitted to support the biosimilarity of MSB11456 to US-Actemra include a 3-way single-dose comparative PK study between SC administered MSB11456, US-Actemra, and EU-RoActemra; a single-dose comparative PK study between IV administered MSB11456 and US-Actemra; and a comparative clinical study of MSB11456 and EU-RoActemra in subjects with RA. In addition, a comparative PK study was conducted with the MSB11456 prefilled syringe (PFS) and autoinjector (AI). A summary of the objectives, designs, study populations, and treatment groups are presented in Table 2.

Table 2. Table Listing All Relevant Submitted Clinical Studies

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Studies					
Study MS200740-0001	NCT03282851	Comparative PK, PD, safety, and immunogenicity of SC administered MSB11456	Randomized, double-blind, parallel-group, single dose	Healthy Subjects, N=685	MSB11456: 231 US-Actemra: 229 EU-RoActemra: 225
Study FKS456-002	Not registered	Comparative PK, safety, and immunogenicity of IV administered MSB11456	Randomized, double-blind, parallel group, single dose	Healthy Subjects, N=128	MSB11456: 62 US-Actemra: 66
Study FKS456-003	Not registered	Comparative PK and safety of PFS and AI presentations of MSB11456	Randomized, open-label, fixed dose, crossover	Healthy Subjects, N=100	PFS-AI: 51 AI-PFS: 49
Comparative Clinical Study					
Study FKS456-001	NCT04512001	Comparative efficacy, safety, and immuno-genicity of repeat SC administration of MSB11456 and EU-RoActemra	Randomized, double-blind, active comparator, 2-arm, parallel group	Moderately to severely active RA, N=604	Core Period (Up to Week 24): MSB11456: 302 EU-RoActemra: 302 Extended Period (Week 24-52): MSB11456: 266 EU-RoActemra: 136 EU-RoActemra /MSB11456: 139

Source: Adapted from Table 1 in the Summary of Clinical Safety and individual clinical study reports

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3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761275 for MSB11456manufactured by Fresenius Kabi USA, LLC. The data submitted in this application are not sufficient to support a conclusion that the manufacture of MSB11456 is well controlled and will lead to a product that is pure and potent for the duration of the shelf-life.

OPQ is recommending that a Complete Response letter be issued to Fresenius Kabi USA, LLC., to outline the deficiencies and the information and data that will be required to support approval. During recent inspections of the Fresenius Kabi Austria GmbH, Austria (FEI 3003708554) and (b) (4) our field inspectors conveyed deficiencies to the representatives of the facilities. Satisfactory resolution of these deficiencies is required before this application may be approved. The CDTL/Division Signatory agree with this assessment and the recommendation for a Complete Response.

3.2. Devices

MSB11456 is available as a 162 mg/0.9 mL single-dose prefilled syringe, a 162 mg/0.9 mL single-dose prefilled auto-injector, and vial presentations (80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL). The PFS with needle safety device is a single use 1 mL glass syringe with a 27G ½ inch (12.7 mm) staked stainless steel needle protected by a rigid needle shield. The needle safety device is based on the (b) (4) passive anti-needle stick device and is composed of a safety device, plunger rod, and extended finger flange with (b) (4) elements. The AI is composed of the PFS inside an (b) (4) AI based on a platform device developed by (b) (4). The AI has a passive anti-needlestick system composed of a needle cover (integral to the body) that automatically covers the needle and locks in extended position after injection is performed and the needle is removed from the skin.

3.2.1. Center for Devices and Radiological Health (CDRH)

CDRH recommends approval based on assessment of device constituent parts of the combination product. See the CDRH review by Kathleen Fitzgerald dated March 7, 2023 for full details.

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

The Applicant provided comparative analyses and a Use-Related Risk Analysis (URRA) to support the use of the MSB11456 PFS and AI devices in the intended patient populations, and the results of human factors (HF) studies for the AI.

Based on the results of the URRA and comparative analyses between the MSB11456 PFS and US-Actemra PFS, DMEPA concluded that results from a HF validation study were not needed to support the MSB11456 PFS. See the DMEPA review by Matthew Barlow dated April 1, 2021 under IND 129965 for full details.

For the MSB11456 AI presentation, DMEPA reviewed the HF validation study and determined that no additional HF data was necessary and the residual risks are

acceptable. Based on the URRA and HF results, DMEPA provided recommendations for AI IFU labeling changes to address the identified medication error concerns and minimize the risk for medication error including:

- Clarify the meaning of "first click" in Step 6.6 given subjective feedback in the HF validation study that some subjects thought that "first click" indicated completion of the injection, which could risk underdosing and reduced therapeutic efficacy.
- Revise Step 9, Figure V to include the language "Date of Administration:" and "Injection Site:" since repeated use of the same site may lead to injection site reactions.

See the DMEPA review memos of Dr. Avani Bhalodia dated April 3 and April 17, 2023, respectively, for full details. In view of the recommendation for a Complete Response, final labeling recommendations will be deferred until the next review cycle, if applicable.

3.3. Office of Study Integrity and Surveillance (OSIS)

Inspections were requested for the clinical site (Auckland Clinical Studies, Auckland, New Zealand) and bioanalytical site ((b) (4)) for Study MS200740-0001. The Office of Study Integrity and Surveillance (OSIS) determined that inspections were not required for either site given the recent Remote Regulatory Assessments for the clinical site in NON-RESPONSIVE under NON-RESPONSIVE and the bioanalytical site in NON-RESPONSIVE under NDA NON-RESPONSIVE. For full details, refer to the OSIS memo by Dr. James Lumalcuri dated October 5, 2022.

An inspection was also requested for the clinical site for Study FKS456-002 (Biokinetica S.A., Jozefow, Poland). OSIS determined that data from the audited site was reliable. For full details, refer to the OSIS memo by Dr. Xikui Chen dated February 27, 2023.

3.4. Office of Scientific Investigations (OSI)

The following clinical study sites were selected from the comparative clinical study FKS456-001 for inspection by the CDER Office of Scientific Investigations (OSI):

- Site #2507 (Dr. Anna Zubrzycka-Sienkiewicz, Warsaw, Poland): enrolled N=21
- Site #2519 (Dr. Maria Misterska-Skora, Wroclaw, Poland): enrolled N=21

These 2 sites were selected for inspection based on the number of enrolled subjects and the fact that these clinical investigator sites were the top 2 sites with the greatest influence on the primary efficacy results. Upon completion of the study site investigations, OSI concluded that, despite some minor protocol deviations and data entry errors, the study appears to have been conducted adequately and that the data generated by these clinical study sites appear acceptable in support of this BLA. The final classification for the two study sites is No Action Indicated (NAI). For full details,

refer to the OSI Clinical Inspection Summary review of Dr. Suyoung Tina Chang dated February 8, 2023.

Author:
Rachel Glaser, M.D.
Cross-Discipline Team Leader (CDTL)

4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

No nonclinical animal studies with MSB11456 were requested or submitted as they were not considered necessary to address any residual uncertainties (see meeting minutes under IND 129965 dated July 14, 2016). In the absence of specific pharmacokinetic, physicochemical, or other identifiable concerns, in vivo assays are not anticipated to provide additional meaningful information to inform the evaluation of toxicity. Animal studies with MSB11456 to US-Actemra were not required to support this 351(k) application.

The main component of the nonclinical review was a safety assessment of extractables and/or leachables of the container closure systems for the MSB11456 drug substance and drug product (for SC and IV administration) and the [(b) (4)] used for [(b) (4)] during manufacturing of MSB11456 drug substance [(b) (4)] There are no nonclinical safety concerns for extractables and leachables based on results from these studies.

4.1.1. Nonclinical Residual Uncertainties Assessment

There were no nonclinical residual uncertainties.

4.2. Product Information

Product Formulation

MSB11456 Drug Product for SC Administration

The MSB11456 drug product for SC administration is a sterile, ready-to-use, single dose solution for injection at a nominal concentration of 180 mg/mL (162 mg/0.9 mL). Table 3 (Applicant's Table) shows the composition of the MSB11456 drug product for SC administration.

The primary container closure system consists of a pre-fillable 1 mL type (b) (4) glass syringe combined with a 27 Gauge, 0.5 inch (12.7 mm) (b) (4) stainless steel needle protected by a rigid needle shield that is closed with a (b) (4) rubber, (b) (4) plunger stopper. The container closure system components comply with the relevant Pharmacopeial monographs and International Organization for Standardization (ISO) standards. The PFS is further permanently assembled into 1) a needle safety device based on the (b) (4) passive anti-needle stick device or 2) an autoinjector (pen) device based on the (b) (4) device.

Table 3. Composition of MSB11456 Drug Product for SC Administration (Applicant's Table)

Ingredient	Function	Quality Standard	Nominal quantity per mL	Nominal quantity per syringe
Tocilizumab	Active ingredient	In-house	180 mg*	162 mg
(b) (4) arginine	(b) (4)	USP, Ph. Eur.	(b) (4) mg	16.7 mg
histidine	Buffering agent	USP, Ph. Eur.	mg	2.0 mg
(b) (4) actic acid	(b) (4)	Ph. Eur.	mg	0.9 mg
Polysorbate 80		NF, Ph. Eur.	0.2 mg	0.2 mg
Sodium chloride		USP, Ph. Eur.	0.6 mg	0.6 mg
Sodium hydroxide**	pH adjustment	NF, Ph. Eur.	q.s. to pH 6.0 ± (b) (4)	
Hydrochloric acid***	pH adjustment	NF, Ph. Eur.	q.s. to pH 6.0 ±	
Water for injection	(b) (4)	USP, Ph. Eur.	(b) (4)	(b) (4)

Ph. Eur. = European Pharmacopoeia, USP = United States Pharmacopoeia, NF = National Formulary; (b) (4) (b) (4)

* (b) (4), refer to Section 3.2.P.2.2 Pharmaceutical Development – Drug Product (PFS) for further details.

** (b) (4)

*** (b) (4)

MSB11456 Drug Product for IV Administration

The MSB11456 drug product for IV administration is a sterile, concentrated solution intended for infusion following dilution in 0.45% or 0.9% sodium chloride at a concentration of 20 mg/mL. The composition of the MSB11456 drug product for IV administration is shown in Table 4 (Applicant's Table).

The primary container closure system consists of a single dose type (b) (4) glass vial closed with a (b) (4) stopper and sealed with an aluminum crimp seal closure. The container closure system components comply with the relevant Pharmacopeial monographs and ISO standards. The MSB11456 drug product for IV administration is available in three strengths which share the same composition and differ only in the size of the vial and the fill volume applied:

- 80 mg/4 mL in 6 (b) (4) vials containing (b) (4) mL formulated drug product. This includes a (b) (4) mL overfill to permit withdrawal of the required volume of not less than 4.0 mL.

- 200 mg/10 mL in 20 (b) (4) vials containing (b) (4) mL formulated drug product. This includes a (b) (4) mL overfill to permit withdrawal of the required volume of not less than 10.0 mL.

- 400 mg/20 mL in 20 (b) (4) vial containing (b) (4) mL formulated drug product. This includes a (b) (4) mL overfill to permit withdrawal of the required volume of not less than 20.0 mL.

Table 4. Composition of MSB11456 Drug Product for IV Administration (Applicant's Table)

Ingredient	Function	Quality Standard	Nominal Quantity per mL
Tocilizumab	Active ingredient	In-house	20 mg*
(b) (4) arginine	(b) (4)	USP, Ph. Eur.	17.4 mg
histidine	Buffering agent	USP, Ph. Eur.	3.1 mg
(b) (4) actic acid	(b) (4)	USP, Ph. Eur.	0.9 mg
Polysorbate 80		NF, Ph. Eur.	0.2 mg
Sodium chloride		USP, Ph. Eur.	0.6 mg
Sodium hydroxide**	pH adjustment	NF, Ph. Eur.	q.s. to pH 6.0 ± (b) (4)
Hydrochloric acid***	pH adjustment	NF, Ph. Eur.	q.s. to pH 6.0 ±
Water for injection	(b) (4)	USP, Ph. Eur.	(b) (4)

Ph. Eur. = European Pharmacopoeia, USP = United States Pharmacopoeia, NF = National Formulary; (b) (4)
(b) (4)

* (b) (4) refer to Section 3.2.P.2.2 Pharmaceutical Development – Drug Product (Vial) for further details.

** (b) (4).

*** (b) (4).

Comments on Excipients

The excipients in the MSB11456 drug product (for both SC and IV administration) include: (b) (4) arginine, (b) (4) histidine, (b) (4) lactic acid, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, and water for injection. There are no novel excipients present in the drug product formulations. The levels of each excipient are within the ranges that are found in FDA-approved SC and IV products.

For comparison, per Section 11 of the ACTEMRA USPI (12/2022):
Each single-dose vial, formulated with a disodium phosphate dodecahydrate/sodium dihydrogen phosphate dihydrate buffered solution, is available at a concentration of 20 mg/mL containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of ACTEMRA. Each mL of solution contains polysorbate 80 (0.5 mg), sucrose (50 mg), and Water for Injection, USP.

Each ready-to-use, single-dose 0.9 mL PFS with a needle safety device or a ready-to-use, single-dose 0.9 mL autoinjector delivers 162 mg tocilizumab, L-arginine hydrochloride (19 mg), L-histidine (1.52 mg), L-histidine hydrochloride monohydrate (1.74 mg), L-methionine (4.03 mg), polysorbate 80 (0.18 mg), and Water for Injection, USP.

Comments on Impurities of Concern

No impurities of concern are identified.

The Applicant conducted extractables and/or leachables studies of the container closure systems for the MSB11456 drug substance and drug product (for SC and IV administration) and the (b) (4) used for (b) (4) during manufacturing of MSB11456 drug substance (b) (4). There are no nonclinical safety concerns for extractables and leachables based on results from these studies (refer to Nonclinical Primary Review dated April 24, 2023 under BLA 761275 in DARRTS [Reference ID: 5163004]).

Authors:

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5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

Table 5. Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	• A PK similarity study (Study MS200740-0001) evaluated PK similarity between MSB11456, EU-RoActemra, and US-Actemra in healthy subjects following SC administration, and another PK study (Study FKS456-002) evaluated PK similarity between MSB11456 and US-Actemra in healthy subjects following IV administration. • PK similarity has been demonstrated between MSB11456 and US-Actemra, and supports a demonstration of no clinically meaningful differences between MSB11456 and US-

Review Issue	Recommendations and Comments
	Actemra for both IV and SC routes of administration. • PK similarity between MSB11456, EU-RoActemra, and US-Actemra provides the PK component of the scientific bridge to support the relevance of comparative data generated using EU-RoActemra to the assessment of biosimilarity.
Immunogenicity	• Similar incidence of ADA and NAb formation was observed between MSB11456, EU-RoActemra and US-Actemra in healthy subjects (Study MS200740-0001) and between MSB11456 and EU-RoActemra in subjects with RA (Study FKS456-001), including following the single transition from EU-RoActemra to MSB11456. Given the scientific bridge was established (based on the analytical and PK comparisons) between MSB11456, US-Actemra, and EU-RoActemra to justify the relevance of data generated with EU-RoActemra as the comparator, these collective immunogenicity results support the assessment of no clinically meaningful differences between MSB11456 and US-Actemra.
Other (specify)	• PK of MSB11456 administered using PFS and AI was comparable.

The clinical development for MSB11456 included 4 clinical studies (see Table 2 in Section 2.2 for details):

In this application, the Applicant seeks the approval of both intravenous (IV) and subcutaneous (SC) routes of administration for MSB11456. Considering the nonlinear pharmacokinetic (PK) characteristics and the differences in systemic exposures between the IV and SC routes of administration, PK similarity assessment is required for both routes of administration.

PK similarity was established in the PK similarity study (Study MS20040-0001) between MSB11456, EU-RoActemra, and US-Actemra. Study MS20040-0001 established the PK component of the scientific bridge to support the relevance of comparative clinical data generated using EU-RoActemra from Study FKS456-001 to the assessment of biosimilarity.

The summaries of the PK similarity findings are given in Table 6 and Table 7. Considering the nonlinear PK characteristics of tocilizumab, the primary PK endpoint is area under the serum drug concentration-time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{last}) for IV administration and AUC_{last} and maximum observed drug concentration (C_{max}) for SC administration.

In the PK similarity study MS200740-0001, the 90% confidence interval (CI) for the least square (LS) geometric means ratios (LS GMRs) for AUC from time 0 to infinity (AUC_{0-inf}), AUC_{last}, and C_{max} were contained within the prespecified criteria of 80 to 125%.

Table 6. Summary of Statistical Analyses for Assessment of PK Similarity Following Subcutaneous Administration (Study MS200740-0001)

Parameter	Geometric Mean (%GeoCV)			Geometric Mean Ratio* (90% CI)		
	MSB11456 N=230	US-Actemra N=226	EU-RoActemra N=224	MSB11456 vs US-Actemra	MSB11456 vs EU-RoActemra	EU-RoActemra vs U.S.-Actemra
Primary						
AUC_{last} (ug.h/mL)	1490 (104.8)	1460 (78.6)	1560 (75.9)	104.15 (93.58, 115.90)	94.78 (85.15, 105.50)	109.88 (98.66, 122.38)
C_{max} (ug/mL)	7.89 (84.2)	7.68 (67.1)	8.26 (63.6)	104.45 (95.05, 114.77)	94.83 (86.28, 104.22)	109.93 (100.16, 121.11)
Secondary						
AUC_{0-inf} (ug.h/mL)	1890 (72.9)	1790 (55.3)	1790 (58.3)	106.16 (96.8, 116.43)	104.03 (94.96, 113.96)	102.05 (93.10, 111.86)

*Presented as percent
Source: Table 11 in Clinical Study Report MS200740-0001

In the PK similarity study FKS456-002, the 90% CI for the LS GMRs for AUC_{last} and AUC_{0-inf} were contained within the prespecified criteria of 80 to 125%.

Table 7. Summary of Statistical Analyses for Assessment of PK Similarity Following Intravenous Administration (Study FKS456-002)

Parameter	Geometric Mean (%GeoCV)		Geometric Mean Ratio* (90% CI)
	MSB11456 N=62	US-Actemra N=66	MSB11456 vs US-Actemra
Primary			
AUC_{last} (ug.h/mL)	28858 (15.3)	27926 (17.2)	103.34 (98.53, 108.37)
Secondary			
$AUC_{0\text{-}inf}$ (ug.h/mL)	31902 (17.2)	30928 (18.9)	103.15% (97.86%, 108.73%)

*Presented as percent
Source: Table 7 and Table 8 in Clinical Study Report FKS456-002

To support the development and approval of auto-injector (AI), the Applicant also conducted one PK comparability study between the MSB11456 pre-filled syringe (PFS) and AI. The summary of the primary and secondary PK endpoints is given in Table 8. The 90% CI for LS GMRs for $AUC_{0\text{-}inf}$, AUC_{last}, and C_{max} were contained within 80% to 125% and supported the comparable exposure between AI and PFS.

Table 8. Summary of Statistical Analyses for Assessment of PK Comparability Between MSB11456 Auto-Injector and Pre-Filled Syringe (Study FKS456-003)

Parameter	Geometric Mean (%GeoCV)		Geometric Mean Ratio* (90% CI)
	MSB11456 Auto-injector N=91	MSB11456 Pre-filled Syringe N=91	MSB11456 Auto-injector vs MSB11456 Pre-filled Syringe
Primary			
AUC_{last} (ug.h/mL)	1524.4 (65)	1463.3 (85)	102.88 (92.21, 114.79)
C_{max} (ug/mL)	8.58 (59.1)	8.47 (68.2)	99.67 (90.95, 109.21)
Secondary			
$AUC_{0\text{-}inf}$ (ug.h/mL)	1604.3 (59)	1595.3 (60)	100.23 (92.67, 108.41)

*Presented as percent
Source: Table 8 in Clinical Study Report FKS456-003

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

PK similarity was shown through the three pair-wise comparisons between MSB11456, US-Actemra, and EU-RoActemra following SC administration (Study MS200740-0001) and the two pair-wise comparisons between MSB11456 and US-Actemra following IV administration (Study FKS456-002).

The clinical studies adequately showed PK similarity between MSB11456 and US-Actemra and showed no increase in immunogenicity risk for MSB11456 when

compared to US-Actemra. There are no residual uncertainties from the clinical pharmacology assessment.

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

In the PK similarity study in healthy subjects, MSB200740-0001, following SC administration of MSB11456, EU-RoActemra, or US-Actemra, the 90% CIs for the GMRs of MSB11456 to EU-RoActemra, MSB11456 to US-Actemra, and EU-RoActemra to US-Actemra for the tested PK parameters (i.e., AUC_{last}, C_{max}, $AUC_{0\text{-}inf}$) were all within the PK similarity acceptance interval of 80% to 125%. These pairwise comparisons met the pre-specified criteria for PK similarity between MSB11456, EU-RoActemra, and US-Actemra; thus, the PK portion of the scientific bridge was established to support the relevance of the data generated using EU-RoActemra.

5.3. Human Pharmacokinetic and Pharmacodynamic Studies

5.3.1. Study MS200740-0001

Clinical Pharmacology Study Design Features

Study MS200740-0001 was a randomized, double-blind, parallel-group, single-dose study to compare the PK/PD of a single 162 mg subcutaneous injection of MSB11456, US-licensed Actemra, or EU-approved RoActemra in healthy adult subjects.

Samples for PK and PD analyses were collected up to 29 days postdose, as well as at the End of Study Assessment visit. Immunogenicity samples were collected at Screening, predose on Day 1, and postdose on Day 15, Day 29, and Day 48 (End of Study visit).

Three hundred and eighteen (318) subjects were initially planned to be randomized (106 subjects per arm). A blinded sample size re-estimation (BSSR) was conducted after 163 subjects completed the study up to Day 29, resulting in an increase of the sample size to 696 subjects.

Clinical Pharmacology Study Endpoints

The primary PK parameters for MSB11456, US-Actemra, and EU-RoActemra comparisons were: AUC_{last} and C_{max}. PK similarity was then assessed for each of the 3 pairwise comparisons with no adjustment for multiplicity since all 3 comparisons needed to demonstrate PK similarity. If the 90% CIs for the geometric LS mean ratio were entirely within the 80.00% to 125.00% prespecified margin for each primary PK

parameter, then PK similarity could be demonstrated.

Bioanalytical PK Method and Performance

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

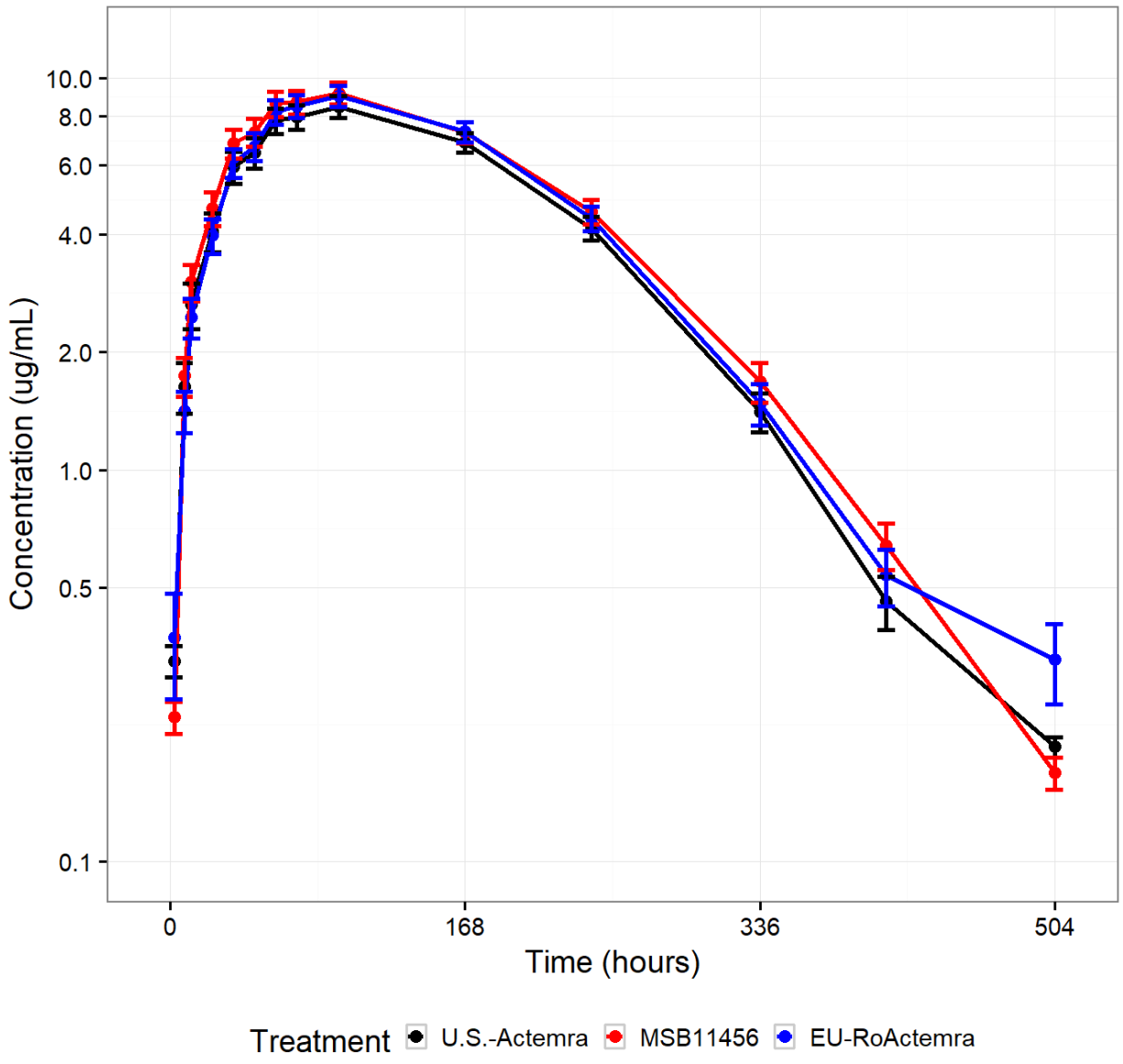
The serum concentrations of MSB11456, US-Actemra, and EU-RoActemra were appropriately quantified using two validated electrochemiluminescence (ECL) assays in Study MSB200740-0001 (validation reports TM.2019 and TM.2272). See detailed information about the assay validation in Appendix 14.3.1.

PK Similarity Assessment

In total, 695 subjects were randomized, and 685 subjects received a single dose of IMP. Ten subjects discontinued prior to treatment, and 666 subjects (97.2%) completed the study.

Mean study drug concentrations over time for all 3 treatment arms are depicted in Figure 1.

Figure 1. Arithmetic Mean (± Standard Error) Study Drug Serum Concentration-Time Profiles for All Treatments on Semi-log Scale



Source: Figure 2 in Clinical Study Report MS200740-0001; reproduced by the reviewer

The PK similarity results are given in Table 6 above. The GMRs and 90% CIs of both AUC_{last} and C_{max} fell in the pre-specified margin of 80% to 125% and supported the conclusion of PK similarity among MSB11456, US-Actemra, and EU-RoActemra following SC administration.

5.3.2. Study FKS456-002

Clinical Pharmacology Study Design Features

Study FKS456-002 was a randomized, single-center, double-blind, 2-arm, parallel-group, single-dose study designed to evaluate PK similarity of MSB11456 with US-licensed Actemra after a single IV infusion of 8 mg/kg for 1 hour in healthy subjects.

Clinical Pharmacology Study Endpoints

The primary PK parameter for MSB11456 and US-Actemra comparisons was: AUC_{last}. For the primary endpoint comparison, the 90% CI for the GMR was derived for the primary PK parameter (AUC_{last}) by exponentiating the 90% CI obtained for the difference between the 2 treatments geometric least squares mean (GLSM) resulting from the ANOVA of the ln-transformed AUC_{last}. PK similarity between the 2 treatments was declared if the 90% CI for the GMR for AUC_{last} laid entirely within the 80.00% to 125.00% prespecified margin.

Bioanalytical PK Method and Performance

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

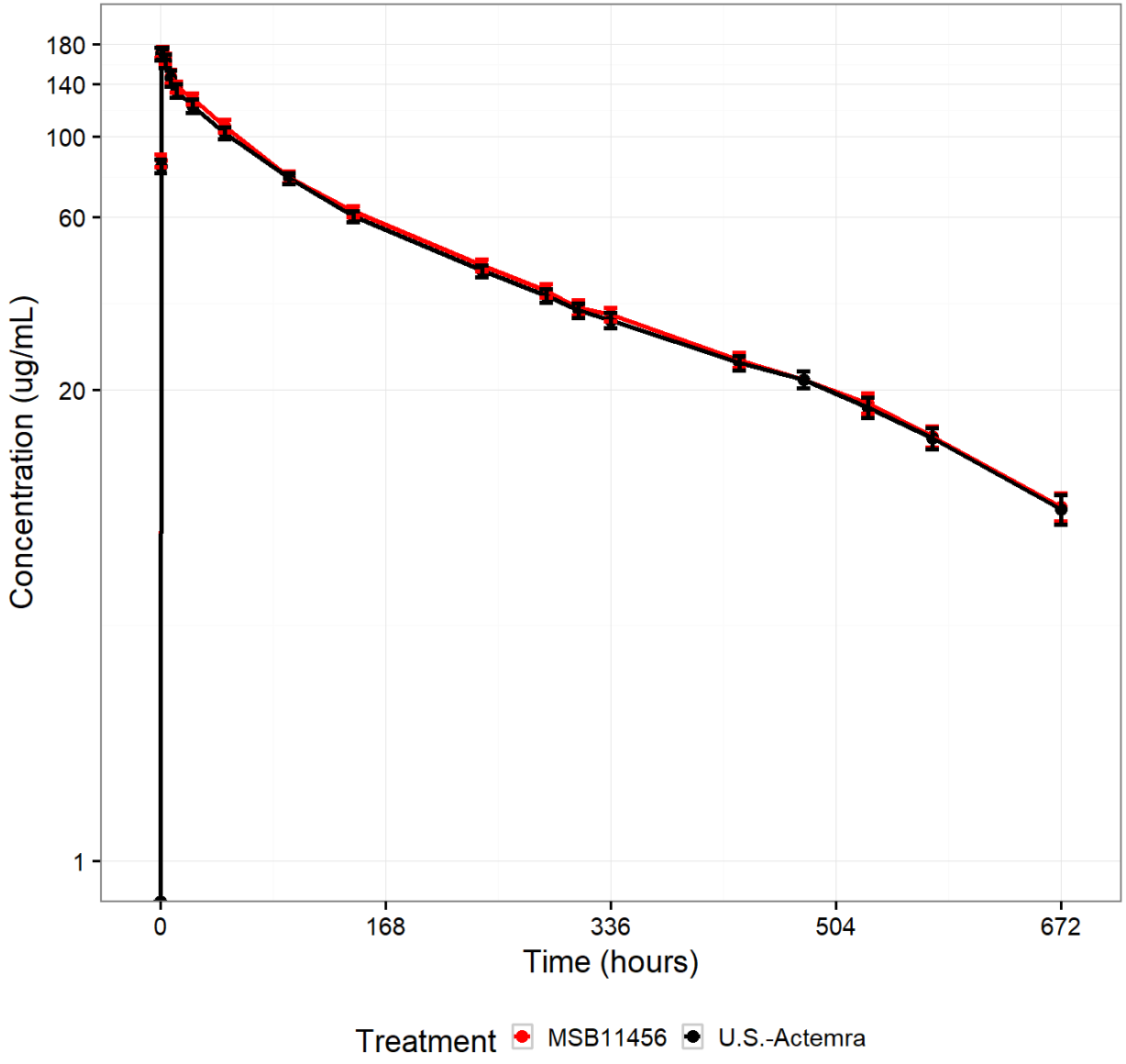
The serum concentrations of MSB11456 and US-Actemra were appropriately quantified using a validated ECL in Study FKS456-002 (validation reports TM.2272). During the method validation, MSB11456 and US-Actemra were used to establish the standard curves, and the accuracy and precision (± 20.0%, ± 25.0% for LLOQ and ULOQ) was evaluated using MSB11456 and US-Actemra as QC samples. See detailed information about the assay validation in Appendix 14.3.1.

PK Similarity Assessment

A total of 130 subjects were randomized. Of them, 2 subjects were withdrawn prior to dosing as an AE occurred after they were randomized. A total of 128 subjects received 1 IV dose of investigational medicinal product (IMP) (8 mg/kg), of which 62 subjects received 1 IV dose of MSB11456 and 66 subjects received 1 IV dose of US-Actemra. All these subjects completed the study.

Mean study drug concentrations over time for both treatment arms are depicted in Figure 2.

Figure 2. Plot of Arithmetic Mean (±Standard Error) Study Drug Serum Concentrations Versus Time on a Semi-log Scale



Source: Figure 2 in Clinical Study Report for Study FKS456-002; reproduced by the reviewer

The PK similarity results are given in Table 7 above. The GMR and 90%CI of AUC_{last} fell in the pre-specified margin of 80% to 125% and supported the conclusion of PK similarity between MSB11456 and US-Actemra following IV administration.

5.3.3. Study FKS456-003

Clinical Pharmacology Study Design Features

Study FKS456-003 was a randomized, open-label, single fixed-dose, 2-treatment, 2-period, cross-over study. The study included a screening period (from Day -28 to Day -3) and 2 treatment periods (i.e., Periods 1 and 2), which were each consisting of: admission to the study site on Day -1, IMP administration on Day 1, discharge from the study site on Day 3, and 11 ambulatory visits up to Day 43. The total duration of the study was approximately 113 days for each subject.

The following IMPs were administered:

- Treatment A: MSB11456 PFS presentation 162 mg SC
- Treatment B: MSB11456 AI presentation 162 mg SC

Clinical Pharmacology Study Endpoints

The primary PK parameters for AI vs. PFS comparisons were: AUC_{last} and C_{max}. The GMR along with corresponding 2-sided 90% CI were estimated for each treatment presentation.

Bioanalytical PK Method and Performance

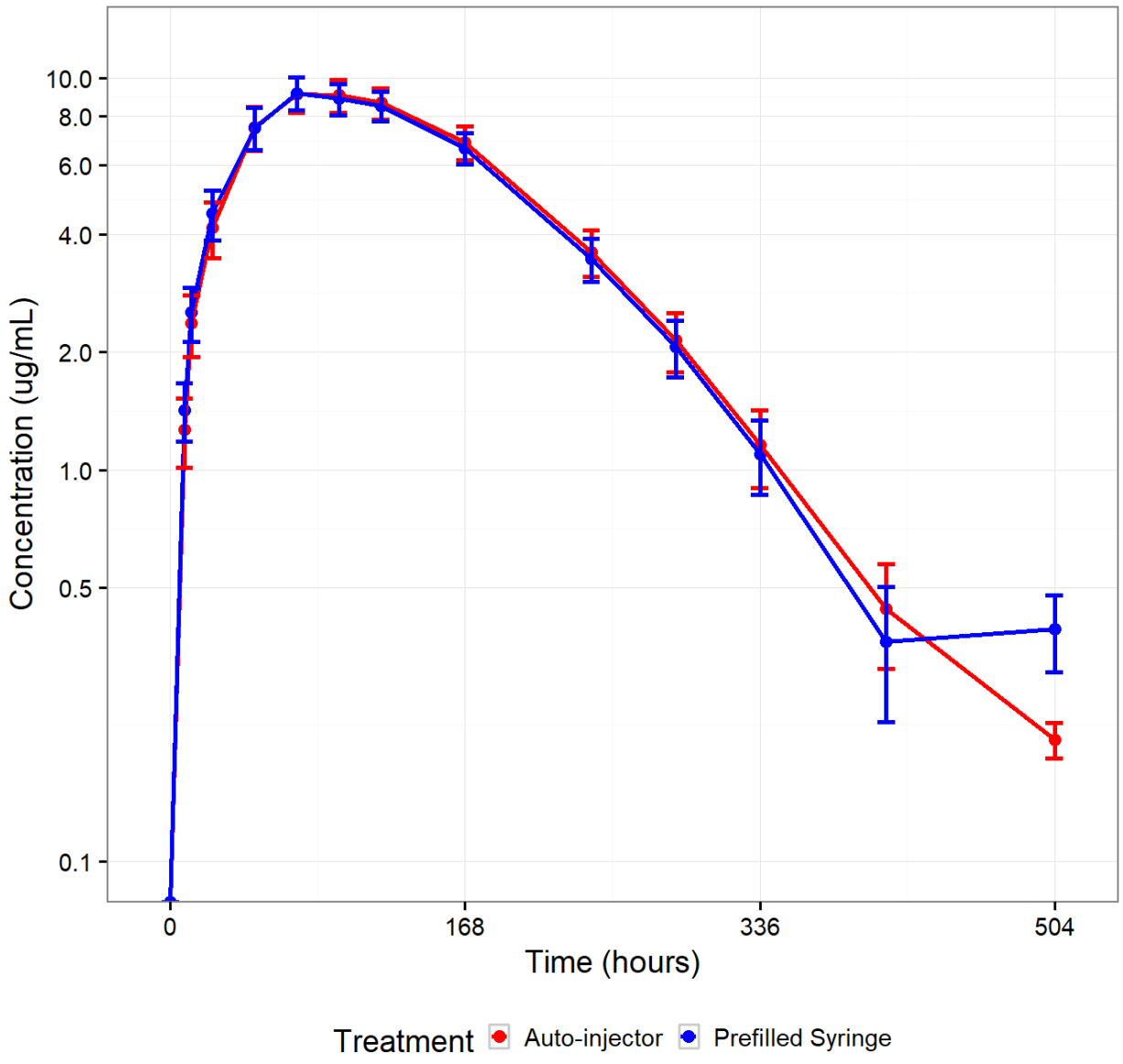
The methodologies used in the analysis of biological samples were sensitive, robust, and fully validated.

The serum concentrations of MSB11456 were appropriately quantified using a validated electrochemiluminescence assay (ECL) in Study FKS456-003 (validation reports TM.2272). During the method validation, MSB11456 was used to establish the standard curves, and the accuracy and precision (± 20.0%, ± 25.0% for LLOQ and ULOQ) was evaluated using MSB11456 as QC samples. See detailed information about the assay validation in Appendix 14.3.2.

PK Comparability Assessment

Mean concentration time profiles following SC administration of MSB11456 via AI and PFS are depicted in Figure 3.

Figure 3. Plot of Arithmetic Mean (±Standard Error) MSB11456 Serum Concentrations versus Time on a Semi-log Scale



Source: Figure 2 in Clinical Study Report for Study FKS456-003; reproduced by the reviewer

The PK comparability results are given in Table 6 above. The GMRs and 90%CIs of both AUC_{last} and C_{max} fell in the range of 80% to 125% and supported the conclusion of PK comparability between MSB11456 AI and PFS following SC administration.

5.4. Clinical Immunogenicity Studies

5.4.1. Study MS200740-0001

Serum immunogenicity samples were collected at baseline, Day 15, Day 29, Day 48 (study termination), as well as early termination visit if applicable, following a single dose SC administration of MSB11456, US-Actemra, and EU-RoActemra. No apparent difference was observed in the overall ADA positivity status (not constrained to treatment-induced positivity) across the 3 treatment arms: 70.1%, 57.2%, 66.7% subjects tested positive overall for MSB11456, US-Actemra, and EU-RoActemra, respectively.

The incidence of treatment-induced ADA positivity was comparable between the 3 treatment arms: 67.1%, 53.7%, 65.8% subjects experienced treatment-induced ADA for MSB11456, US-Actemra, and EU-RoActemra, respectively.

Overall, 2.6% in the MSB11456 arm, 1.3% in the US-Actemra arm, and 2.7% in the EU-RoActemra arm tested positive for NAb. The incidence of NAb against study drug was similar across the 3 treatment arms.

5.4.2. Study FKS456-002

Serum immunogenicity samples were collected at baseline, Day 15, Day 29, Day 48 (study termination), as well as early termination visit if applicable, following a single dose IV administration of MSB11456 and US-Actemra. 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). All subjects with post-dose ADAs had a treatment-induced ADA status, as their pre-dose samples were negative and at least 1 post-dose sample was positive.

There was no notable difference in overall NAb incidence between MSB11456 (in 4 out of 57 [7.0%] subjects) and US-Actemra (in 8 out of 65 [12.3%] subjects).

5.4.3. Study FKS456-001

Immunogenicity upon repeated SC dosing was evaluated in Study FKS456-001.

Design features of the clinical immunogenicity assessment

Study FKS456-001 was a multicenter, randomized (1:1), active-controlled, double-blind, multiple fixed-dose, multinational, 2-arm, parallel-group study to compare the efficacy, safety, and immunogenicity of the proposed biosimilar candidate MSB11456 versus EU-RoActemra in subjects with moderately to severely active rheumatoid arthritis.

The study has a duration of up to 67 weeks, including a Screening Period of up to 28 days, a double-blind 24-week Core Treatment Period (Day 1 to Week 24) (hereafter generally referred to as the Core Period), an additional 28-week double-blind Extended Treatment Period (Week 24 to Week 52) (hereafter generally referred to as the Extended Period), and a 12-week Safety Evaluation Period (Week 51 to Week 63).

At Week 24, after all efficacy and safety assessments were performed, subjects remaining on IMP entered the Extended Period. Subjects who were originally randomized to receive EU-RoActemra were re-randomized in a 1:1 ratio to continue their weekly treatment with EU-RoActemra or transitioned to MSB11456 (EU-RoActemra/MSB11456 arm) starting at Week 24. Subjects who were originally randomized to MSB11456 were re-assigned to continue the same treatment (with a probability of 1) during the Extended Period (MSB11456 group). During the Extended Period, subjects received a total of 28 doses of either EU-RoActemra or MSB11456 (1 dose at each of Weeks 24 to 51, inclusive).

Bioanalytical PK Method and Performance

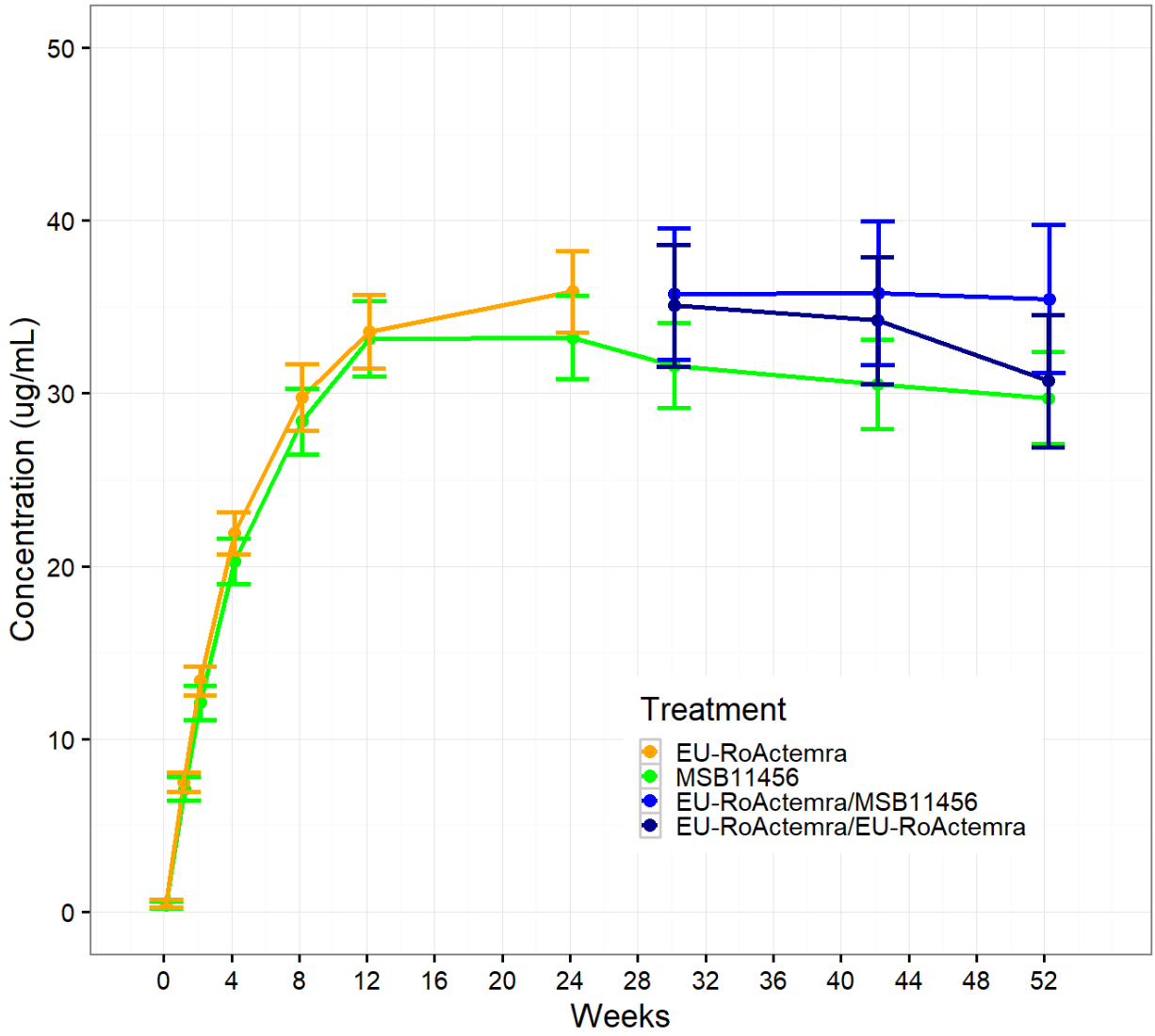
The methodologies used in the analysis of biological samples were sensitive, robust, and fully validated.

The serum concentrations of MSB11456 and EU-RoActemra were appropriately quantified using a validated ECL in Study FKS456-001 (validation reports TM.2272). During the method validation, MSB11456 and EU-RoActemra was used to establish the standard curves, and the accuracy and precision (± 20.0%, ± 25.0% for LLOQ and ULOQ) was evaluated using MSB11456 and EU-RoActemra as QC samples. See detailed information about the assay validation in Appendix 14.3.1.

PK Assessment

In the comparative clinical study FSK456-001, trough PK samples were collected. The average of observed trough concentrations at each sampling time point are depicted in Figure 4 below. No meaningful differences were observed.

Figure 4. Mean Trough Concentration over Time (Linear Scale)



Source: Reviewer's analysis

The PK profiles appear similar between MSB11456 and EU-RoActemra. After the single transition at Week 24, no differences in trough study drug concentrations were observed between subjects who transitioned from EU-RoActemra to MSB11456 and subjects who continued on EU-RoActemra.

Immunogenicity endpoints

Anti-drug antibodies (ADA) and neutralizing antibodies (NAb) were selected as the immunogenicity endpoints. Descriptive statistics were summarized for the incidence of ADA and NAb and the ADA titers.

Immunogenicity assay's capability of detecting the ADA and NAb in the presence of proposed product and non-U.S.-licensed comparator product in the study samples

The ADA response to study drug were detected using a validated ECL assay in Study FKS456-001 (Method TM.2502, validation reports 14714.061319).

The tolerance levels were as follows:

Monoclonal:

- The assay could not determine drug tolerance levels for MSB11456 at the positive control level 1 (PCL-1, 3.00 ng/mL) concentration, and was tolerant to 400 µg/mL at the positive control high (PCH, 500 ng/mL) level. However, it can be concluded that the assay is tolerant up to 25.0 µg/mL at PCL-1 through the inhibition comparability evaluation which is comparable to the comparator drugs.
- The assay showed drug tolerance to US-Actemra at 50.0 µg/mL for the PCL-1 concentration and was tolerant to 400 µg/mL at the PCH level.
- The assay showed drug tolerance to EU-RoActemra at 25.0 µg/mL for the PCL-1 concentration and was tolerant to 400 µg/mL at the PCH level.

Polyclonal:

- The assay showed drug tolerance to MSB11456 at 25.0 µg/mL at the PCL-1 (5.00 ng/mL) concentration, and was tolerant to 400 µg/mL at the PCH (1000 ng/mL) level.
- The assay showed drug tolerance to US-Actemra at 25.0 µg/mL for the PCL-1 concentration and was tolerant to 400 µg/mL at the PCH level.
- The assay showed drug tolerance to EU-RoActemra at 25.0 µg/mL for the PCL-1 concentration and was tolerant to 400 µg/mL at the PCH level.

The NAb against study drug were detected using a validated cell-based assay in Study FKS456-001 (Method TM.2504, validation reports 14445.230419).

For MSB11456 comparative clinical study lot, the assay was tolerant up to 15.0 µg/mL at the PCH antibody level (15 ug/mL) and 1.00 µg/mL at the PCL level (3.75 ug/mL). For US-Actemra and EU-RoActemra, the assay is tolerant up to 30.0 µg/mL at the PCH antibody level and 1.00 µg/mL at the PCL level.

Refer to the Office of Biotechnology Products Immunogenicity review for the assessment of ADA and NAb assay methods.

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

Blood samples for ADA and NAb assay were collected in Study FKS456-001 from Week 0 to Week 52. ADA and Nab samples were collected with serum PK samples at each timepoint. The last dose, either MSB11456 or EU-RoActemra, was administered at

Week 51. The last ADA and NAb samples were collected 4 weeks after the last dose at Week 55, however, no PK samples were collected at Week 55.

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

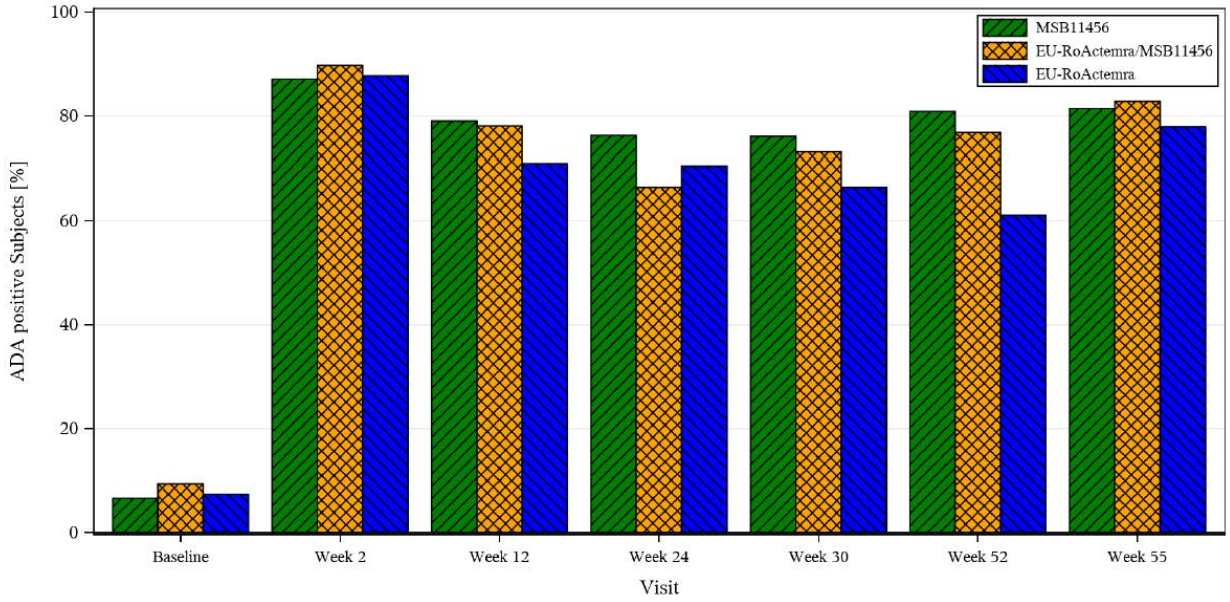
The number and percent of ADA and NAb positive subjects are listed in Table 9, and the time course of ADA development is depicted in Figure 5 and Figure 6. ADA incidence and ADA titers were similar between MSB11456 and EU-RoActemra up to Week 24 before the single transition. After the single transition at Week 24, the ADA incidence remained similar among subjects who continued on MSB11456, subjects who transitioned from EU-RoActemra to MSB11456, and subjects who continued on EU-RoActemra. While the ADA titers were about 1-fold higher in subjects who continued on MSB11456 and subjects who transitioned from EU-RoActemra to MSB11456 compared to subjects who continued on EU-RoActemra, this observation was not considered to be meaningful.

Table 9. Immunogenicity Results for Binding ADA and NAb in Study FKS456-001, Core Period

	N	Anti-Drug antibody		NAb
		Baseline	Treatment-Induced	
MSB11456	302	20/302 (6.6%)	284/299 (95.0%)	25/299 (8.4%)
EU-RoActemra	302	25/302 (8.3%)	278/301 (92.4%)	33/301 (11.0%)

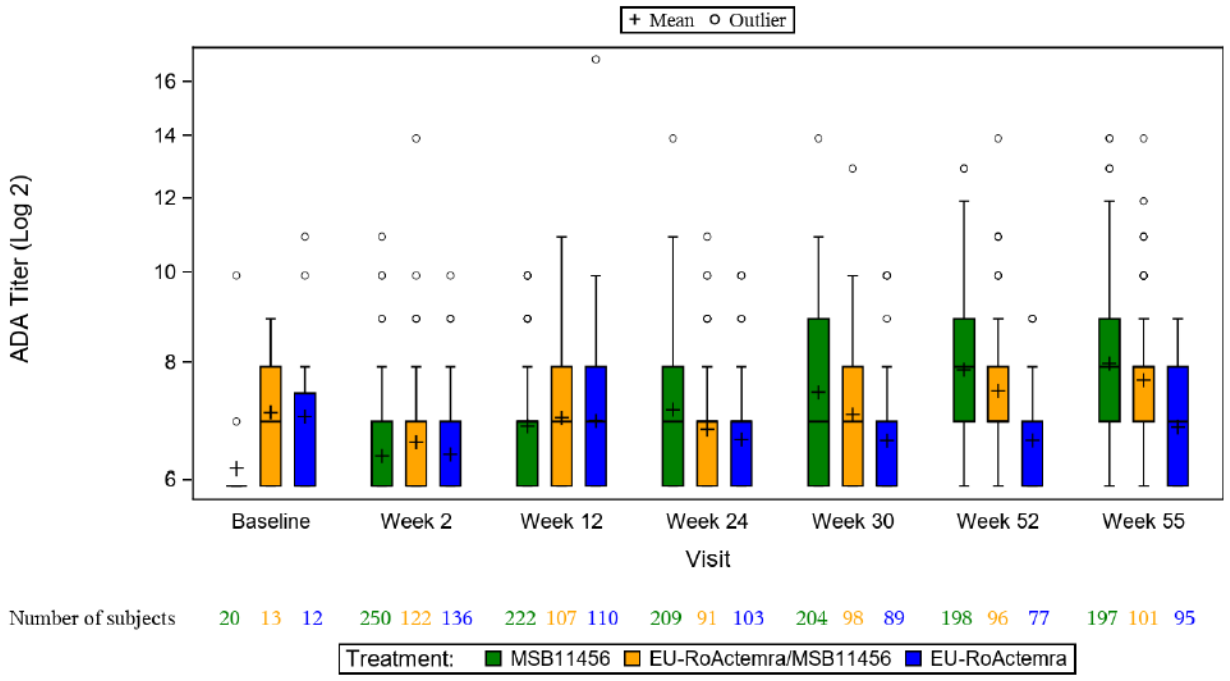
Treatment-induced ADA status was defined as follows:
In subjects with an ADA-negative predose sample, a treatment-induced ADA response was defined as any postdose sample being positive in the ADA confirmatory assay
In subjects with an ADA-positive predose sample, a treatment-induced ADA response was defined as a 1.808-fold increase (the minimum significant ratio) in titers from the predose assessment to a postdose assessment
Source: Applicant analysis; Table 51 and Table 14.2.8.2.1 in the Clinical Study Report for Study FKS456-001

Figure 5: Antidrug Antibody Incidence, Overall Period, Safety Analysis Set



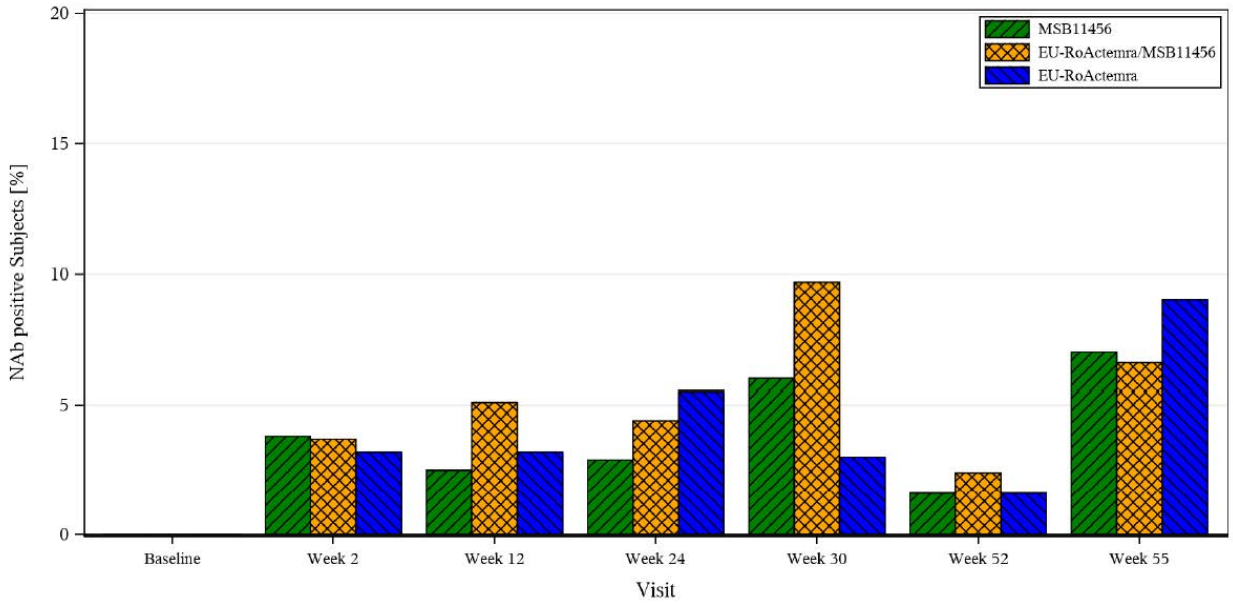
Source: Figure 5 in Week 55 Clinical Study Report for Study FKS456-001

Figure 6. Antidrug Antibody Titer, Box Plot, Overall Period, Safety Analysis Set



Source: Figure 6 in Clinical Study Report for Study FKS456-001 (Week 55)

Figure 7. Neutralizing Antibody Incidence, Overall Period, Safety Analysis Set



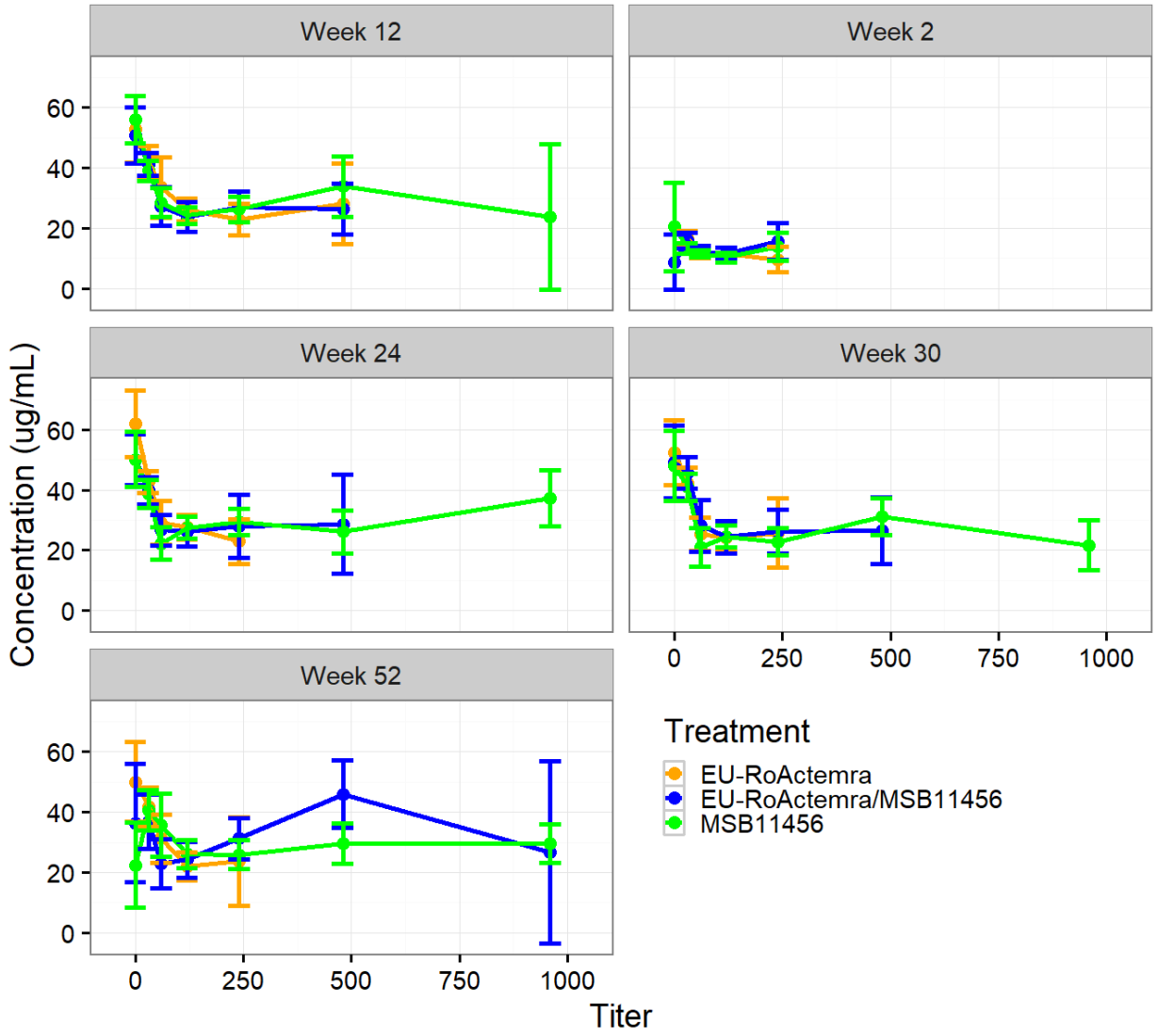
Source: Figure 7 in Week 55 Clinical Study Report for Study FKS456-001

In conclusion, the development of ADA and NAb are comparable between MSB11446 and EU-RoActemra. There was no increase in ADA positive incidence following the single transition at Week 24, however the single transition from EU-RoActemra to MSB11456 resulted in numerically higher ADA titers from Week 30 to Week 55 and numerically higher NAb incidence at Week 30. As discussed below, the increase in ADA titer and NAb was not associated with an impact on PK, efficacy, or safety.

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

The impact of ADA development on study drug PK is depicted in Figure 8. Study drug trough concentrations appear to be ADA titer dependent at Week 2, Week 12, and Week 24 following multiple dose administration of MSB11456 and EU-RoActemra, and at Week 30 and Week 52 after the single transition. The observed trough concentrations were lower in subjects with higher ADA titer, and no further decrease in trough concentrations was observed in subjects with ADA titer higher than 120. The impact of ADA titer on study drug concentration was similar between MSB11456 and EU-RoActemra. Also, the ADA titer effect on study drug concentration was similar among MSB11456, EU-RoActemra, and the single transition at Week 24 (EU-RoActemra transitioned to MSB11456).

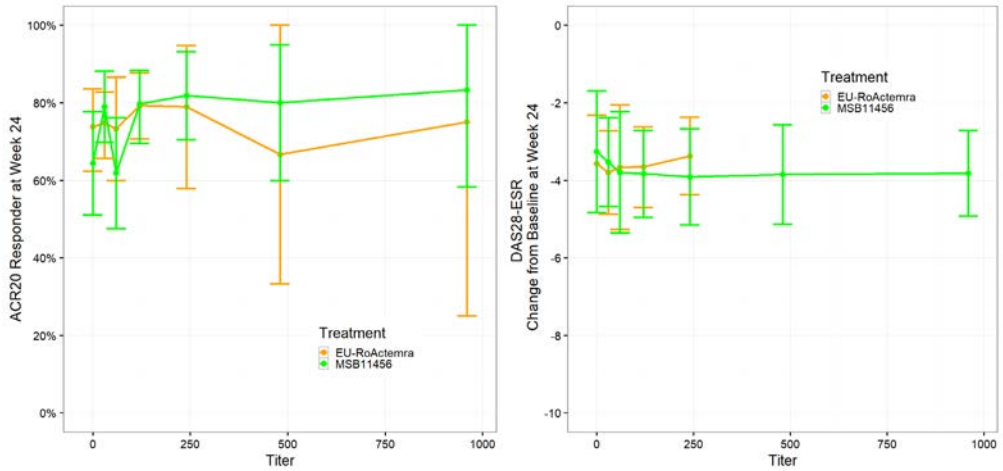
Figure 8. Consistent Anti-Drug Antibody Effect on Pharmacokinetics



Source: Reviewer's Analysis

The development of ADA has no impact on clinical efficacy endpoints ACR20 responder rate at Week 24 and DAS28-ESR change from baseline at Week 24 (Figure 9).

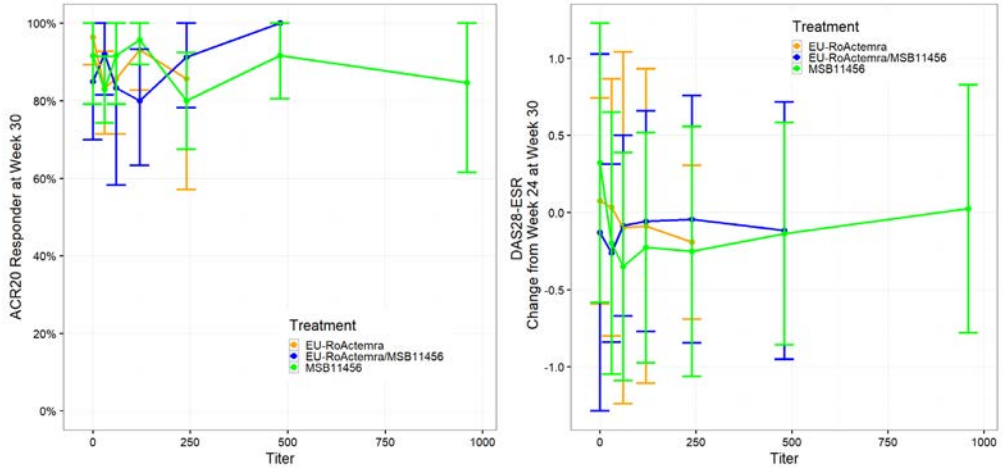
Figure 9. Lack of Anti-Drug Antibody Effect on Clinical Efficacy Between MSB11456 and EU-RoActemra at Week 24



Source: Reviewer's Analysis

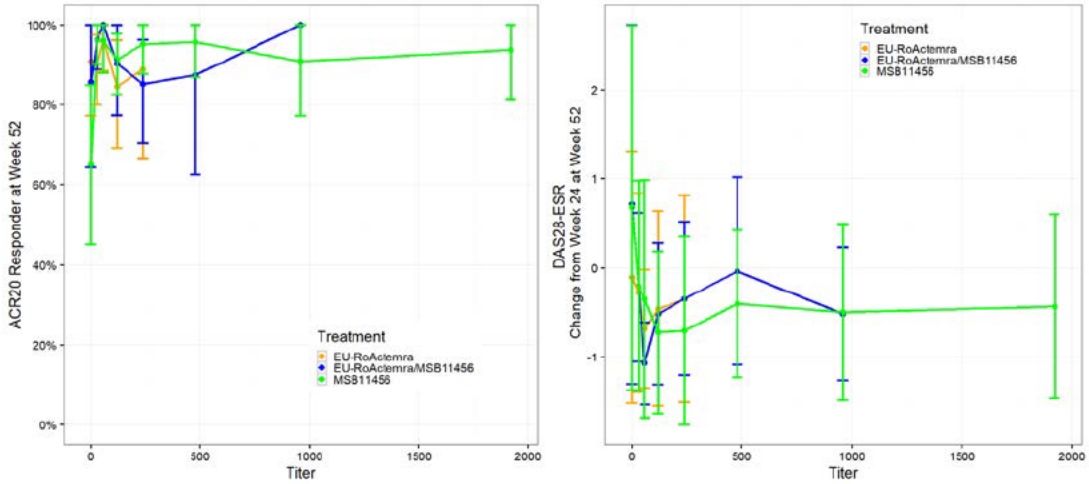
Similarly, the impact of the single transition at Week 24 did not change the clinical efficacy responses at Week 30 and Week 52 (Figure 10 and Figure 11).

Figure 10. Lack of Anti-Drug Antibody Effect on Clinical Efficacy at Week 30 after the Single Transition at Week 24



Source: Reviewer's Analysis

Figure 11. Lack of Anti-Drug Antibody Effect on Clinical Efficacy at Week 52 after the Single Transition at Week 24



Source: Reviewer's Analysis

Also, the development of NAb had no effect on clinical efficacy endpoints at Week 24 as well as at Week 30 after the single transition (Table 10).

Table 10. Lack of Neutralizing Antibody Effect on Clinical Efficacy

Core Period (Week 24)				Extended Period (Week 30)			
Treatment	NAb	ACR20	DAS28-ESR change from baseline	Treatment	NAb	ACR20	DAS28-ESR change from Week 24
EU-RoActemra	Positive (N=13)	80.2%	-3.65	EU-RoActemra	Positive (N=4)	100%	-0.425
	Negative	85.4%	-3.65	EU-RoActemra	Negative	82.7%	0.053
				MSB11456	Positive (N=19)	100%	-0.300
				MSB11456	Negative	88.8%	-0.128
MSB11456	Positive (N=8)	75%	-3.53	MSB11456	Positive (N=23)	91.3%	-0.252
	Negative	78.6%	-3.69	MSB11456	Negative	89.6%	-0.063

Source: Reviewer's Analysis

In conclusion, the ADA effect on study drug PK was similar between MSB11456 and EU-RoActemra. No ADA or NAb effect on clinical efficacy was observed in both MSB11456 and EU-RoActemra arms.

Impact of ADA and NAb on safety

In Study FKS456-001, treatment-induced ADA (and NAb) were observed in 95.0% (11.0 %) of subjects on MSB11456 and 92.4% (8.4%) of subjects receiving EU-RoActemra, up to Week 24. Up to Week 30, ADA (and NAb) incidence was 97.0% (13.4%) for the MSB11456 arm, 95.7% (12.3%) for the EU-RoActemra arm, and 97.1 % (20.1%) for the EU-RoActemra/MSB11456 treatment arm.

During the Core Period and the Extended Period from Weeks 24 to 30, the incidences of TEAEs and AESIs were generally similar between the treatment arms, and between ADA positive and ADA negative subjects. TE-SAEs in the Core Period were similar between treatment arms, and more frequently reported by ADA negative subjects (MSB11456: 20.0%; EU-RoActemra: 25.0%) than ADA positive subjects (MSB11456: 8.5%; EU-RoActemra: 9.3%). Few TE-SAEs were reported in the Extended Period from Weeks 24 to 30, including 4 ADA positive/NAb negative MSB11456-treated subjects, 1 ADA/NAb positive EU-RoActemra-treated subject, and no subjects in the EU-RoActemra/MSB11456 arm. TEAEs, AESI, and TE-SAEs were similar or lower in NAb positive subjects compared to NAb negative subjects in both the Core Period and the Extended Period from Weeks 24 to 30. There was no increase in TEAEs, AESI, or TE-SAEs in subjects who underwent a single transition from EU-RoActemra to MSB11456 as compared to subjects who continued on EU-RoActemra or MSB11456.

A greater proportion of subjects had injection site reactions (ISR) in the MSB11456 arm (11.3%) than the EU-RoActemra arm (4.6%) during the Core Period. Between Weeks 24 and 30, ISR were low and occurred in similar proportions of subjects (MSB11456: 2.0%; EU-RoActemra/MSB11456: 1.0%; and EU-RoActemra: 0) and did not increase in subjects who transitioned from EU-RoActemra to MSB11456. Through Week 30, the overall frequencies of ISR were generally higher in ADA positive (MSB11456: 11.4%; EU-RoActemra 6.5%; EU-RoActemra/MSB11456: 5.2%) than ADA negative subjects (MSB11456: 16.7%; EU-RoActemra: 0; EU-RoActemra/MSB11456: 0) and in NAb positive subjects (MSB11456: 12.5%; EU-RoActemra: 15.0%; EU-RoActemra/MSB11456: 7.1%) than NAb negative subjects (MSB11456: 11.5%; EU-RoActemra: 4.9%; EU-RoActemra/MSB11456: 4.5%). All ISR were Grade 1 or Grade 2 in severity. There was no increase in ISR in ADA and NAb positive subjects from Weeks 24 to 30 in the EU-RoActemra/MSB11456 arm compared to the MSB11456 and EU-RoActemra arms that continued treatment.

There were no TEAEs of anaphylaxis, and one ADA negative MSB11456-treated subject had Grade 2 drug hypersensitivity during the Core Period. From Weeks 24 to 30, there were no TEAEs of anaphylaxis or hypersensitivity. Hypersensitivity and anaphylactic reactions were also assessed by SMQ analysis. Based on SMQ analysis,

there were no anaphylactic reactions during the Core or Extended Periods through Week 55. During the Core Period, SMQ analysis of hypersensitivity identified similar proportions of subjects in the ADA positive subgroup (MSB11456: 3.5% EU-RoActemra: 5.5%) and ADA negative subgroup (MSB11456: 6.7%; EU-RoActemra: 0). Following the single transition, SMQ analysis for hypersensitivity identified similar proportions of ADA positive subjects in each treatment arm (MSB11456: 2.0%; EU-RoActemra: 2.3%; EU-RoActemra/MSB11456: 3.1%), while no ADA negative subjects in any treatment arm had events. There were no events of anaphylaxis and a single TEAE of hypersensitivity in Study FKS456-001. SMQ hypersensitivity TEAEs were generally similar by ADA status during the Core Period. Few SMQ hypersensitivity TEAEs were reported from Weeks 24 to 30, and all occurred in ADA positive subjects. There was no increase in subjects in the single transition arm compared to those who continued treatment without transition.

The majority of subjects with safety events through Week 30 were ADA positive, consistent with the prevalence of ADA positive subjects in the study (93.0%). The proportions of subjects with potential immune-related safety events, including events of ISR and hypersensitivity, were small and did not increase following the single transition. The assessment of the impact of ADA on safety is limited by the small numbers of ADA negative subjects in the study. However, no apparent impact of immunogenicity on safety was observed.

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6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

Comparative Efficacy: Study FKS456-001 was a randomized, double-blind, multiple-dose, parallel-group, two-arm study to evaluate the efficacy, safety, and immunogenicity of subcutaneously administered MSB11456 compared to EU-RoActemra in 604 subjects with moderately to severely active rheumatoid arthritis. The primary endpoint was the mean change from baseline in Disease Activity Score-28 Erythrocyte Sedimentation Rate (DAS28-ESR) at Week 24. The key secondary endpoint was based on 20% improvement in American College of Rheumatology (ACR) Core Set Measurements (ACR20) response rate at Week 24.

At Week 24, the estimated mean change from baseline in DAS28-ESR was -3.53 in the MSB11456 treatment arm compared to -3.54 in the EU-RoActemra arm. The 90% confidence interval for the difference of treatment effects between the MSB11456 and

EU-RoActemra groups was (-0.16, 0.18) which is contained within the prespecified similarity margin of [-0.6, 0.5], agreed upon with the Agency. Supportive and sensitivity analyses of DAS28-ESR change from baseline at Week 24, and analyses of key secondary endpoints, including ACR20 response rate at Week 24, and DAS28-ESR change from baseline at Week 12, were similar between the treatment arms. The results based on the primary and key secondary endpoints support the finding of no meaningful differences in efficacy between MSB11456 and EU-RoActemra.

Comparative Safety and Immunogenicity: The comparative safety evaluation plan for MSB11456 reflected the known safety profile of US-Actemra as described in the USPI and other published data. Given that the Applicant submitted adequate data to establish the scientific bridge to justify the relevance of data generated with EU-RoActemra as the comparator, the submitted safety and immunogenicity data from Study FKS456-001 supported by the data from the single-dose PK studies MS200740-0001 and FKS456-002, are adequate to support the demonstration of no clinically meaningful differences in safety and immunogenicity between MSB11456 and US-Actemra.

The safety database comprised data from a total of 1517 subjects from the four clinical studies, including 913 healthy subjects (MS20074-0001, FSK456-002, FSK456-003) and 604 subjects with RA (FKS456-001) who received at least 1 dose of MSB11456, EU-RoActemra, or US-Actemra. Of these, 331 healthy subjects received SC MSB11456, 62 healthy subjects received IV MSB11456, and 441 subjects with RA were exposed to SC MSB11456. The size of the safety database is adequate to provide a reliable descriptive comparison between the products.

The safety risks identified are consistent with the known adverse event profile of US-Actemra. Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, adverse events leading to IMP discontinuation, and development of anti-drug antibodies (ADA) were generally similar between the treatment groups in the comparative clinical study FKS456-001. In addition, a single transition of non-treatment naïve subjects to the proposed biosimilar, i.e., subjects previously treated with EU-RoActemra to MSB11456, did not result in an increase in ADA or immune-related adverse events. A small numerical increase in NAb was observed in the EU-RoActemra/MSB11456 arm compared to the EU-RoActemra and MSB11456 arms following the single transition, however, no differences in PK, efficacy, or safety were observed.

The safety observed in healthy subjects in the comparative PK studies further supports comparable safety profiles for MSB11456, EU-RoActemra and, where applicable, US-Actemra. Additionally, the safety for MSB11456 was similar to the comparator product(s) when administered by SC and IV administration, and similar when administered by PFS or AI.

Overall, the collective evidence from the comparative clinical study, and the supportive safety data from the single-dose PK studies, supports a demonstration of no clinically

meaningful differences between MSB11456 and US-Actemra, as the Applicant provided adequate data to establish the scientific bridge between MSB11456, US-Actemra, and EU-RoActemra to justify the relevance of data generated with EU-RoActemra to the assessment of biosimilarity.

6.1.1. Comparative Safety and Immunogenicity: Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the clinical and statistical analyses.

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

6.2.1. Study FKS456-001

Study FKS456-001 was a randomized, double-blind, multiple-dose, parallel-group, two-arm study designed to evaluate the efficacy, safety, and immunogenicity of MSB11456 compared to EU-RoActemra in subjects with moderately to severely active rheumatoid arthritis with an inadequate response to methotrexate therapy.

Data and Analysis Quality

There are no concerns regarding data quality and integrity.

Data Sources

In the original submission of BLA 761275 received on May 31, 2022, the Applicant submitted a document package and datasets for Study FKS456-001 in Clinical Study Report (CSR) version 1.0 dated March 28, 2022, which includes data up to and including Week 30 (Week 30 CSR). On October 11, 2022, FDA received an updated document package for this study from the Applicant that included the Clinical Study Report Version 1.0 dated September 9, 2022, which includes data up to and including Week 55 (Week 55 CSR). The Statistical Review Team noted several places where analysis results pertaining to the Core Period of the study reported in the Week 30 CSR differed from those reported in the Week 55 CSR. In response to an information request (IR) dated November 23, 2022, the Applicant submitted explanations for these differences and submitted an updated data package to support the analysis results in the Week 55 CSR. This statistical review is based on the Week 55 CSR (in sequence 0009 of the submission) and the supporting datasets for the Week 55 CSR (in sequence 0014 of the submission).

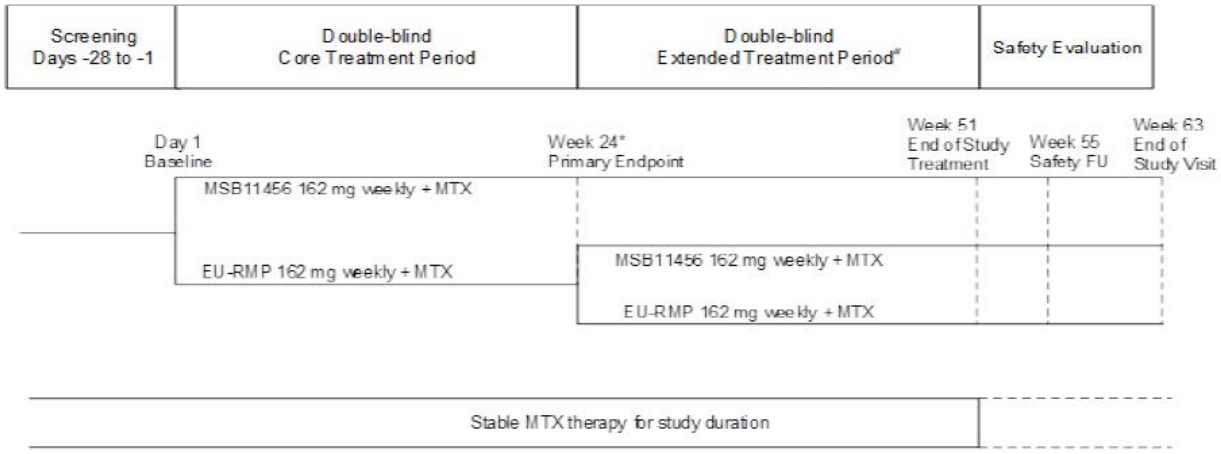
Study Design and Endpoints

Overall Design

Study FKS456-001 was a multicenter, randomized, active-controlled, double-blind, multiple fixed-dose, multinational, two-arm, parallel-group study designed to compare the efficacy, safety, and immunogenicity of MSB11456 versus EU-RoActemra in subjects with moderately to severely active RA with an inadequate response to methotrexate. Eligible subjects had an inadequate response to 1 or more DMARDs (conventional and up to 2 biologic DMARDs) and were receiving a stable dose of methotrexate for at least 8 weeks and treated for at least 12 consecutive weeks prior to randomization. The population of subjects with previous exposure to any biologic treatment was capped at 10% of the total study population, and subjects who previously received more than 2 biologic treatments for RA were excluded. All subjects were required to continue on stable background methotrexate throughout the treatment periods. Oral corticosteroids ≤ 10 mg/day prednisone or equivalent were permitted provided that the dose had been stable for at least 6 weeks prior to randomization.

The study consisted of two treatment periods and a safety follow up period, as described below. Figure 12 presents the overall study design.

Figure 12. Study Design Schematic for Study FKS456-001



Source: Figure 1, Week 55 Clinical Study Report for Study FKS456-001

Core Period: Subjects were randomized 1:1 to receive 162 mg SC administered MSB11456 or EU-RoActemra weekly for 24 weeks. Randomization was stratified by previous exposure to biologic treatment for RA (yes/no).

Extended Period: Subjects who completed the Core Period received an additional 28 weeks of treatment with IMP. The Extended Period design included a blinded single transition in which subjects treated with EU-RoActemra in the Core Period were re-randomized 1:1 to either continue EU-RoActemra or to undergo a single transition to

MSB11456 (EU-RoActemra/MSB11456 treatment arm). Subjects treated with MSB11456 in the Core Period continued to receive MSB11456.

Safety Evaluation Period: Subjects who completed the Extended Period were followed after receiving the final dose of IMP at Week 51 for an additional 12 weeks off treatment up to Week 63.

The primary endpoint for Study FKS456-001 was the mean absolute change from baseline in Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR) at Week 24. The DAS28-ESR is a continuous composite endpoint with differential weighting given to each of the following components:

- Tender Joint Count (28 joints)
- Swollen Joint Count (28 joints)
- Patient's Global Assessment of Disease Activity
- Erythrocyte sedimentation rate (ESR)

The key secondary efficacy endpoint for Study FKS456-001 was the 20% improvement in American College of Rheumatology Core Set Measurements (ACR20) response rate at Week 24.

Study Location

Study FKS456-001 was a multinational study. Subjects were enrolled from 81 sites in Bulgaria, Czech Republic, Georgia, Hungary, Moldova, Poland, Russia, Serbia, and Slovakia.

Study Subjects

Key Inclusion Criteria

Adult subjects with moderately to severely active RA on a stable dose of methotrexate and previously with an inadequate response to one or more DMARDs were defined by the following criteria:

- ≥ 18 years of age
- Body weight < 100 kg
- Diagnosis of RA based on the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Classification Criteria with a disease duration of ≥ 6 months at screening
- Moderately to severely active RA as defined by:
    - Swollen Joint Count ≥ 6 (66 joint count) and Tender Joint Count ≥ 6 (68 joint count) at screening and randomization
    - Radiographic evidence of ≥ 1 joint with a definite erosion attributable to RA at screening. The radiographic evidence of joint erosion had to be no older than 6 months

  - CRP ≥ 1 mg/dL (≥ 10 mg/L) and/or ESR ≥ 28 mm/hour at screening
- Treated with methotrexate (oral and/or subcutaneously administered) for at least 12 consecutive weeks immediately prior to randomization and on a stable dose between 10 and 25 mg/week for 8 weeks prior to screening
- Was willing to receive at least 5 mg/week or equivalent of folic acid
- Previous inadequate clinical response to at least 1 DMARD (either conventional or up to 2 biologics)
- Withdrawn off all DMARDs other than methotrexate at least 8 weeks prior to randomization with the exception of leflunomide, which must have been discontinued ≥ 12 weeks prior to randomization (or ≥ 4 weeks after 11 days of standard cholestyramine washout)
- Discontinued biologic treatment for ≥ 12 weeks prior to randomization

Key Exclusion Criteria

- ACR functional class IV or wheelchair/bedbound
- Rheumatic autoimmune disease or history of/current inflammatory joint disease other than RA or significant systemic involvement secondary to RA (e.g., Felty's syndrome, vasculitis, pulmonary fibrosis, gout, Lyme disease, psoriatic arthritis). Sjogren's syndrome secondary to RA was allowed.
- Previously received tocilizumab, an investigational or licensed biosimilar to tocilizumab, or any IL-6 acting drugs (approved or investigational)
- Prior use of targeted synthetic DMARDs including Janus kinase inhibitors (e.g., tofacitinib, baricitinib, upadacitinib or investigational e.g., filgotinib, peficitinib)
- Prior use of more than 2 biologic treatments for RA
- Prior use of biologic investigational drugs (excluding biosimilars) for the treatment of RA
- Previous treatment with any alkylating agents (e.g. cyclophosphamide, chlorambucil) or cell-depleting therapies (e.g., alemtuzumab, rituximab), including investigational drugs or approved biosimilars, or previous total lymphoid irradiation
- Used nonsteroidal anti-inflammatory drugs (NSAIDs) at a non-stable dose within 4 weeks prior to randomization or exceeded the maximum recommended dose. Note: Subjects were permitted to take aspirin at a dose of ≤ 325 mg daily for cardiac prophylaxis. Use of paracetamol was also allowed in the study.
- Use of oral corticosteroids > 10 mg/day prednisone or equivalent if the dose had not been stable for at least 6 weeks prior to randomization.
- Intra-articular or parenteral corticosteroids within 4 weeks prior to randomization
- Use of high potency opioid analgesics
- Treated with intravenous gamma globulin or plasmapheresis within 6 months of randomization
- History of diverticulosis that required antibiotic treatment or any other gastrointestinal condition (e.g., inflammatory bowel disease, mechanic bowel

obstruction, hernia) that could predispose the patient to gastrointestinal perforations

- Laboratory abnormalities (excluding ESR and CRP values) considered clinically significant by the Investigator or any of the following at screening:
    - Hemoglobin < 8 g/dL for women or 8.5 g/dL for men
    - White blood cells < 3.5 x 10^9/L
    - Absolute neutrophil count < 2.0 x 10^9/L
    - Platelet count < 100 x 10^9/L
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 times the upper limit of normal (ULN)
    - Creatinine > 1.5 mg/dL if the patient was aged < 65 years old, or > the upper limit of normal if the patient was aged ≥ 65 years old or proteinuria ≥ 3+ by dipstick
    - Creatinine clearance < 50 mL/min (Cockcroft-Gault formula)

Study Treatments

MSB11456 or EU-RoActemra 162 mg SC was administered weekly. During the Core Period, subjects were assigned to receive 24 total doses of MSB11456 or EU-RoActemra. In the Extended Period, subjects were assigned to receive an additional 28 total doses of MSB11456 or EU-RoActemra.

IMP was supplied in single-use pre-filled syringes containing 162 mg (0.9 mL) of MSB11456 or EU-RoActemra. The recommended injection site was the lower part of the abdomen below the navel, except for the 5 cm area directly around the navel. The first three doses of IMP (Days 1, 8 and 15) were administered by a trained healthcare professional on site on to ensure that the subject or their caregiver was appropriately trained for subsequent at-home administration. At the discretion of the Investigator, subsequent weekly doses of IMP were self-administered or administered by a trained caregiver. Written instructions on proper dosage, administrating, storage, and recording were provided to subjects. Dispensed IMP was returned to the study site at each follow up visit.

Predefined members of the Applicant team were unblinded at the time of the Week 30 results. Details as to who would be unblinded for the Week 30 analysis and reporting, including the regulatory dossier and submissions, were given in a Data Access Plan, which was finalized before the Week 30 unblinding was performed. Those unblinded for the Week 30 primary analysis, including specific contract research organization (CRO) and Sponsor personnel, did not make any further decisions for the study until after the study was fully unblinded for the Week 55 analysis. Study team members working on the Week 55 CSR and program team members working on submission activities were unblinded following a Week 55 partial database freeze of all study data, except for the NAb data. The rest of the main study team at the Sponsor and CRO, along with subjects, investigators, and site personnel remained blinded up to the Week 55

unblinding, following complete Week 55 database freeze, including receipt of the NAb data.

Medications

Permitted Medications

- Methotrexate: all eligible subjects were required to be a on a dose between 10 and 25 mg per week (oral or subcutaneous) throughout both the Core and Extended Periods. Temporary interruptions up to 14 days or for two doses were allowed for safety reasons. Dose reductions and interruptions for methotrexate-related side effects could occur at the Investigator's discretion.
- Folic acid: a stable dose ≥ 5 mg per week total, either as a single dose or as daily doses according to local guidelines.
- Oral corticosteroids: doses ≤ 10 mg per day prednisone or equivalent were permitted if the dose had been stable for at least 6 weeks prior to randomization. However, dose increases in dose for the treatment of RA were not permitted.
- Intra-articular corticosteroids: a single intra-articular injection of corticosteroids not exceeding 40 mg triamcinolone or equivalent could be injected into no more than 1 joint between Weeks 24 and 52.
- NSAIDs: use up to the maximum recommended dose was permitted throughout the study, provided that the dose had been stable for at least 4 weeks prior to randomization. Dose increases were not permitted, but dose reduction or discontinuations were allowed. Aspirin at a dose of ≤ 325 mg daily was allowed for cardiac prophylaxis. All subjects on NSAIDs were required to use proton pump inhibitors or histamine subtype-2 receptor blockers at recommended doses according to local standards of care.
- Analgesics other than NSAIDs: low potency opioid analgesics (codeine, hydrocodone, tramadol, and tapentadol) were permitted at doses up to 40 mg of morphine equivalent. Other analgesics up to the maximum recommended dose were also permitted. However, use was strongly discouraged within 24 hours prior to a study visit at which efficacy was assessed.
- Contraception: the protocol included contraceptive guidelines for men and women of childbearing potential. Women of childbearing potential and female subjects whose menopausal status was in doubt used highly effective contraception (i.e. methods with a failure rate of less than 1% per year) bilateral tubal occlusion, a vasectomized partner, or total abstinence. Men were either surgically sterile (vasectomy or documented aspermia) or agreed to use a condom with spermicide and have their female partners of childbearing potential agree to use highly effective contraception from the time of the first administration of study drug and for at least 3 months after the last dose of IMP.
- Hormone replacement therapy: permitted for female subjects only if already being taken at study entry, i.e. initiation during the study was not permitted.

- COVID-19 vaccination: COVID-19 vaccination was permitted only after Week 30 and preferably right after the Week 30 or Week 42 visits. To ensure the development of an adequate immune response to the vaccine, subjects were advised to interrupt study treatment 1 week before and after each dose of vaccine. COVID-19 vaccination was not permitted from 4 weeks prior to randomization until completion of the Week 30 visit.

Prohibited Medications

- More than 2 different biological immunomodulating agents
- Alkylating agents or cell-depleting therapies, including investigational drugs or approved biosimilars
- Targeted synthetic DMARDs or biological agent for a condition other than RA
- Conventional synthetic DMARDs other than methotrexate
- Intra-articular or parenteral corticosteroid injections until Week 24
- High potency opioid analgesics (e.g. methadone, hydromorphone, oxycodone, fentanyl, or morphine)
- Intravenous gamma globulin or plasmapheresis
- Live or attenuated vaccines

Individual IMP Discontinuation and Study Withdrawal

IMP had to be discontinued for the following:

- Adverse event
    - Adverse events that in the judgment of the Investigator prevented the subject from continuing treatment
    - If a subject developed serious infection, gastrointestinal perforation, serious complications of diverticulitis, hypersensitivity reaction (including anaphylaxis), demyelinating disorder, active hepatic disease, and hepatic impairment
    - Any laboratory abnormalities that in the judgement of the Investigator prevented the subject from continuing treatment
    - Potential Hy's Law events
    - Anaphylactic or other serious allergic reactions
    - If study drug could not be resumed due to a toxicity and/or in case of toxicity that unacceptably endangers the safety of the subject
- Lost to follow-up
- Protocol non-compliance including any protocol deviations that resulted in a significant risk to the subject's safety if treatment continued, including the use of prohibited treatment, following discussion with the Medical Monitor
- Lack of efficacy
- Pregnancy
- Death
- Withdrawal of consent from treatment

- Principal Investigator's decision (i.e. the Investigator thought that continuation would be detrimental to the subject's well-being)
- Quantiferon®-TB Gold Plus test negative at randomization, but subsequently positive at Week 24

Subjects who discontinued IMP for any of above reasons were still followed for efficacy and safety assessments and not considered withdrawn from the study.

Study drug was re-introduced if the cause of study drug interruption was solved and the re-start of treatment was considered medically justified and not otherwise prohibited (e.g., treatment with prohibited medication), with the approval of the Medical Monitor.

Subjects were removed from the study for the following:
- Adverse event
- Lost to follow-up
- Death
- Withdrawal of consent
- Other

Statistical Methodologies

Analysis Sets

The Applicant defined the Intent-To-Treat (ITT), Safety, and Per-Protocol (PP) Analysis Sets as follows.

- **ITT Analysis Set:** All randomized subjects. Subjects were analyzed according to their randomized treatment.

- **Week 24 PP Analysis Set:** All randomized and treated subjects (hence a subgroup of the ITT Analysis Set) who completed the Core 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.

  A clinically important protocol deviation was a major deviation (a deviation that had a major impact on data quality or patient safety or led to death) likely to affect the efficacy of treatment. Subjects were analyzed according to their randomized and received treatment, as receipt of a different treatment from that assigned was a clinically important protocol deviation.

- **Week 12 PP Analysis Set:** All randomized and treated subjects 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.

- **Safety Analysis Set:** All subjects who received at least 1 dose of IMP (MSB11456 or EU-RoActemra) during the Core Period.

Primary Analysis

The Primary Analysis (DAS28-ESR Intent-to-Treat [ITT]) targeted the effect of IMP on the variable measurement regardless of adherence to the IMP or to the protocol, including use of prohibited medication prior to Week 24.

The change from baseline at Week 24 in DAS28-ESR was analyzed 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 Interactive Response Technology (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) for the EMA and its 90% CI for the FDA.

- For the FDA: MSB11456 was considered similar to EU-RoActemra if the 90% CI for the difference in mean change from baseline to Week 24 in DAS28-ESR between MSB11456 and EU-RoActemra laid entirely within the similarity margins of [-0.6, 0.5].

- For the EMA: MSB11456 was considered similar to EU-RoActemra if the 95% CI for the difference in mean change from baseline to Week 24 in DAS28-ESR between MSB11456 and EU-RoActemra laid entirely within the similarity margins of [-0.6, 0.6].

The primary analysis was based on the Core Period using the ITT Analysis Set.

Primary Analysis Imputation Methods

Missing DAS28-ESR scores at Week 24 were imputed by a multiple imputation procedure. Nonmonotone missing data (i.e., interim missing DAS28-ESR scores for subjects who had missed visits/endpoints but had returned for next visit) were assumed to missing at random (MAR) and were imputed separately for each treatment group using the Markov chain Monte Carlo option of SAS PROC MI. Then the monotone missing values for each treatment group were imputed via the chained equation method, using SAS PROC MI option MONOTONE REG. First, all missing data for the first postbaseline 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. The number of imputations was set to (b) (4) and the PROC MI steps always used the seed of (b) (4). Missing values for DAS28-ESR score were imputed at each

postbaseline visit. Baseline DAS28-ESR score, and the randomization 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.

Key Secondary Analysis

The Key Secondary Analysis (ACR20 ITT) targeted the effect of IMP on the variable measurement regardless of adherence to the IMP or to the protocol, including use of prohibited medication prior to 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 a similarity margin of [-15%, 15%]. Mantel-Haenszel weights were used to combine the stratum components.

This key secondary analysis was performed on the ITT Analysis Set.

Key Secondary Analysis Imputation Methods

Missing ACR20 response data were imputed using the last observation carried forward (LOCF) method. All missing ACR20 assessments were imputed using the last nonmissing assessment. Subjects who had just a baseline assessment had their postbaseline assessments imputed as nonresponders.

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.

Supportive Analysis of Week 12

Supportive Analysis of Week12-DAS28-ESR change from baseline had the same attributes as the Primary Analysis, except that Week 24 was replaced by Week 12 in all relevant attributes' description.

Sample Size Information

A sample size of 542 randomized subjects (271 subjects per arm) was chosen to provide approximately 460 subjects (230 per arm) in the PP Analysis Set at Week 24, assuming a 15% drop-out rate (including major protocol deviations).

For the FDA:

- A total of 460 evaluable subjects (230 per arm) would provide 90% power to demonstrate similarity between treatments for the primary endpoint, with similarity margins of [-0.6, 0.5] and a Type I error of 5%, assuming no difference between the 2 treatment groups and a common standard deviation of 1.76.

For the EMA:

- A total of 460 evaluable subjects (230 per arm) would provide 90% power to demonstrate similarity between treatments for the primary endpoint, with similarity 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 similarity margins [-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 statistical reviewer calculated that for the primary endpoint, with 460 subjects (230 per arm), using the Applicant's assumptions labeled "For the FDA", the power is approximately 89.64%, and using the Applicant's assumptions labeled as "For the EMA", the power is approximately 90.86%. Separately for the ACR20 endpoint, using the Applicant's assumptions, the reviewer calculated that with 460 subjects (230 per arm) the power is approximately 81.43%. As described in the Week 55 CSR, the Applicant planned for 10% over-enrollment of 596 subjects which was slightly exceeded (604 subjects were enrolled).

Similarity Margins

The SAP discusses the similarity margins and includes the following information.

In the absence of innovator studies comparing the weekly subcutaneous dosing regimen versus placebo, the dataset used to build the statistical assumptions has been extrapolated from the pivotal studies with the intravenous presentation. The subcutaneous 162 mg weekly regimen was shown to have comparable efficacy and safety to the intravenous presentation at a dose of 8 mg / kg every 4 weeks (Burmester, 2014).

In order to be in line with both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) requirements, different acceptance margins are predefined for the primary endpoint mean change from baseline in Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR) at Week 24.

Similarity margins of ± 0.6, correspond to the retention of approximately 65% of conservative estimates of treatment effect sizes relative to placebo for EU-RoActemra, based on the upper bound of 95% confidence interval from a meta-analysis performed by the Sponsor. The metaanalysis was performed using the following publications: Genovese, 2008; Smolen, 2008; Kremer, 2011; Emery, 2008. The similarity margins defined respectively for FDA and EMA are specified below:

- For the FDA, the similarity margins are set to [-0.6, 0.5]. The FDA has recommended a stricter margin using 0.5 as the upper bound (FDA electronic correspondence October 19, 2016). To help with the study feasibility the lower bound is set to -0.6. A change of -0.6 in favor of MSB11456 is seen as a non-clinically significant difference as long as the safety and immunogenicity profile of MSB11456 demonstrates no more risk than EU-RoActemra.

- For the EMA, the similarity margins are set to ± 0.6.

Specificities of Secondary Efficacy Endpoint “ACR20 at W24”: The treatment difference in American College of Rheumatology (ACR)20 at W24 will be assessed versus predefined margins. The similarity margins are set to ±15%. These proposed similarity margins correspond to 50% retention of conservative estimates of the effect size of EU-RoActemra relative to placebo (derived from Genovese, 2008; Smolen, 2008; Kremer, 2011; Emery, 2008 using meta-analysis).

Subject Disposition

During the Screening Period, 908 individuals were screened, and 604 subjects were randomized to treatment. A total of 302 subjects received MSB11456, and 302 subjects received EU-RoActemra in the Core Period. All 604 randomized subjects received IMP administered subcutaneously according to assigned treatment and were included in the ITT and Safety Analysis Sets.

The proportions of subjects completing treatment through the Core Period were generally balanced by treatment arm (MSB11456: 88.4%; EU-Ro-Actemra 91.4%) with 11.9% of subjects in the MSB11456 arm and 8.9% of subjects in the EU-RoActemra arm, respectively, discontinuing IMP prior to Week 24 (Figure 13). Subjects could have had more than 1 reason for discontinuing IMP; the most frequently reported reasons were adverse event (MSB11456: 7.0%; EU-RoActemra: 5.3%) and withdrawal of consent from treatment (MSB11456: 5.3%; EU-RoActemra: 3.0%).

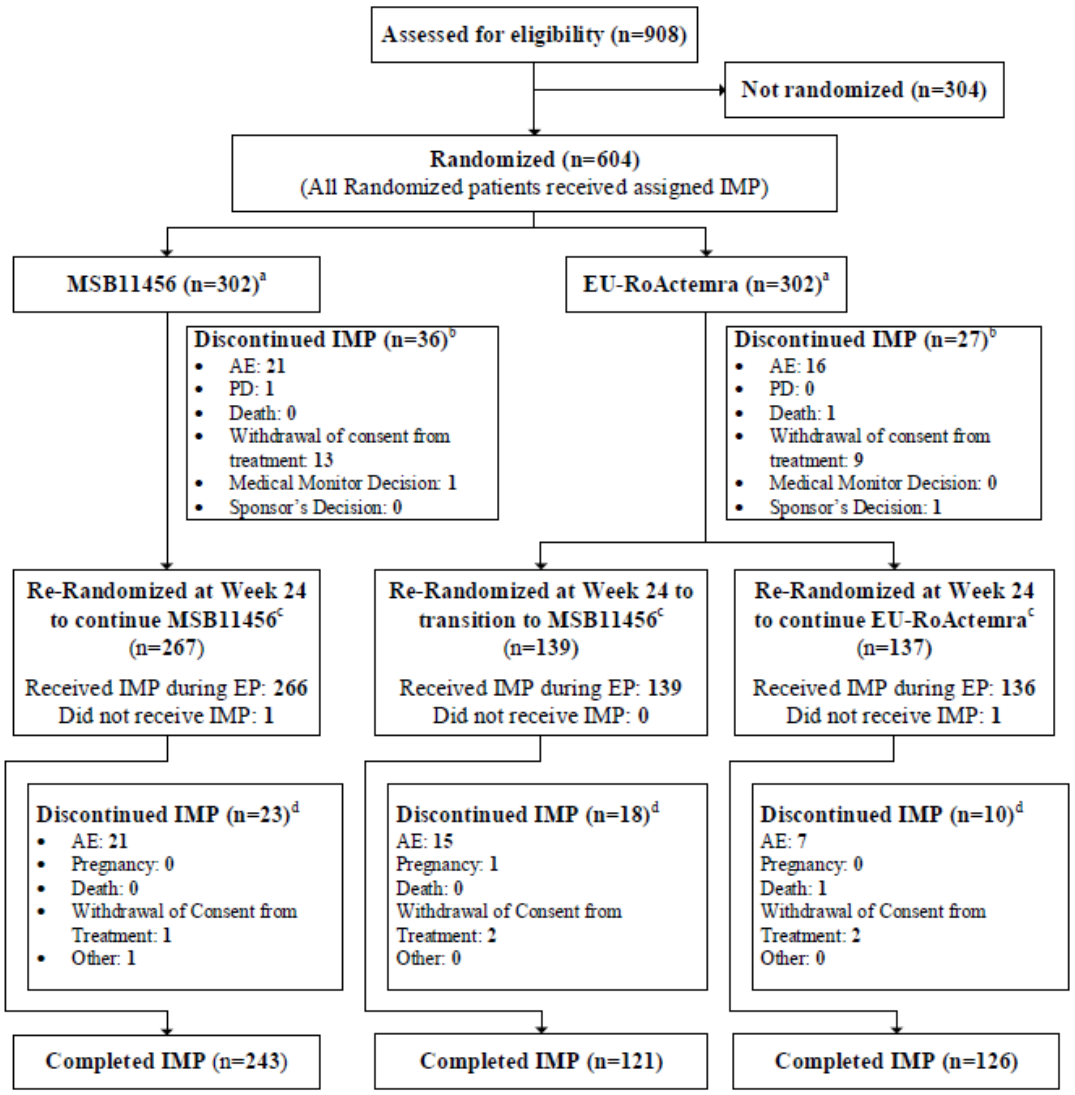
Similar proportions of subjects in the MSB11456 (88.4%) and EU-RoActemra (91.4%) arms were assigned treatment in the Extended Treatment Period. Subjects were required to have a negative mycobacterium tuberculosis complex (TB) test at Week 24 to be eligible to receive IMP in the Extended Period. As a result, 20 subjects in the ITT Analysis Set who converted to a positive TB test, balanced by treatment arm

(MSB11456: 3.6%; EU-RoActemra: 3.0%), were discontinued from IMP consistent with the protocol specified IMP Discontinuation criteria. Eighteen (18) of the 20 subjects tested positive for TB at Week 24 and were considered adverse events in the Core Period. The remaining 2 subjects had their positive tests collected after Week 24 and were considered adverse events in the Extended Period; these were also considered protocol violations. See the safety discussion under “Dropouts and Discontinuations” in Section 6.3.2 for additional details.

Similar proportions of subjects in the MSB11456 (8.6%) and EU-RoActemra (7.4%) arms, and a numerically greater proportion of subjects in the EU-RoActemra/MSB11456 arm (12.9%) discontinued IMP in the Extended Period. The most common reason for IMP discontinuation in the Extended Period was adverse event, which was reported by a numerically greater proportion of subjects in the EU-RoActemra/MSB11456 arm (10.8%) compared to the MSB11456 (7.9%) and EU-RoActemra (5.1%) arms. Other reasons for IMP discontinuation were reported for few subjects and generally balanced by arm (Figure 13).

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 a major deviation likely to affect the efficacy of treatment. Major protocol deviations were generally balanced by treatment arms in both treatment periods. The most common deviations, both in the Core (MSB11456: 18.5%; EU-RoActemra: 20.2%) and Extended (MSB11456: 15.4%; EU-RoActemra: 19.0%; EU-RoActemra/MSB11456: 13.7%) Periods, respectively, were related to laboratory assessments. Other common deviations in the Core Period were related to visit schedule (MSB11456: 17.5%; EU-RoActemra 10.6%) and concomitant medication use (MSB11456: 11.9%; EU-RoActemra: 9.3%). During the Core Period, similar proportions of subjects in each arm had at least 1 major protocol deviation leading to the subject’s exclusion from the Week 24 PP Analysis Set; these were most commonly deviations related to the visit schedule. Full disposition outcomes for the ITT, Safety, and PP Analysis Sets are presented in Table 11.

Figure 13. Subject Disposition in Study FKS456-001, ITT Analysis Set



AE = adverse event, EP = Extended Period, EU-RoActemra = European Union–approved RoActemra, IMP = investigational medicinal product, PD = protocol deviation; RMP = reference medicinal product
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.
[c] Extended Period and Overall Period: MSB11456, RMP-to-MSB11456, and RMP groups.
[d] Patients discontinued IMP within the Extended Period after re-randomization.
Sources: Table 14.1.1.1.1, Table 14.1.1.3.1, and Table 14.1.1.3.3

Source: Figure 2 of the Week 55 Clinical Study Report for Study FKS456-001

Table 11. Statistical Reviewer's Summary of ITT, Safety, and Per Protocol Analysis Sets Based on Applicant's Subject Level Dataset (ADSL_IR)

Analysis Set Reason for Exclusion [n]	MSB11456	EU-RoActemra	Total
Subjects Screened			908
Not Randomized			304
Reason Not Randomized*			
Adverse Event			1
Clinical Team Did Not Agree To Give More Time For Screening, Due To Patient Was Ill And Could Not Come To Site In Proper Time.			1
Death			1
Due To Covid19			2
Patient Did Not Come For Randomization Visit In The Visit Window			1
Patient Missed Randomization Window.			1
The Patient Changes Own Telephone Number , So We Could Not To Contact With Patient. So Randomization Was Not Performed.			1
Trial Screen Failure			289
Withdrawal Of Consent From Study			7
Randomized: ITT Analysis Set	302	302	604
Safety Analysis Set	302	302	604
Week 24 PP Analysis Set	247	250	497
Reasons for Exclusions from PP Analysis Set**			
Clinically Important Protocol Deviation	3	4	7
Clinically Important Protocol Deviation/ Treatment Compliance < 80% in Core Period	1	0	1
Did not complete	2	2	4
MTX Compliance < 80% in Core Period	10	18	28
Treatment Compliance < 80% in Core Period	9	8	17
Treatment Compliance < 80% in Core Period/ Did not complete	20	12	32
Treatment Compliance < 80% in Core Period/ MTX Compliance < 80% in Core Period	4	2	6
Treatment Compliance < 80% in Core Period/ MTX Compliance < 80% in Core Period/ Did not complete	6	6	12
Week 12 PP Analysis Set	261	267	528
Reasons for Exclusions from PP Analysis Set**			
Clinically Important Protocol Deviation	2	3	5
Clinically Important Protocol Deviation/ Treatment Compliance < 80% in Core Period	1	0	1
Clinically Important Protocol Deviation/ Treatment Compliance < 80% in Core Period/ Did not complete	0	1	1
Did not complete	3	1	4
MTX Compliance < 80% in Core Period	4	7	11
Treatment Compliance < 80% in Core Period	13	14	27
Treatment Compliance < 80% in Core Period/ Did not complete	14	7	21
Treatment Compliance < 80% in Core Period/ MTX Compliance < 80% in Core Period	2	1	3

Treatment Compliance < 80% in Core Period/ MTX Compliance < 80% in Core Period/ Did not complete	2	1	3

*The reasons not randomized are written here as they are provided in the ADSL_IR dataset.
**The reasons for exclusion from the PP Analysis Set are written here as they are stated in the ADSL_IR dataset. Subjects excluded from the Week PP Analysis Set because of multiple reasons are only counted here one time in the appropriate row that lists all applicable exclusion reasons.
Source: Statistical Reviewer

Demographics and Baseline Characteristics

Summaries of demographic characteristics and baseline disease characteristics are shown in Table 12 and on baseline disease characteristics shown in was generated by both statistical and clinical reviewers (see the footnote of Table 13 for details).

Subject demographics and anthropometric variables were similar across the two treatment arms. The majority of subjects were female (82.5%) with a mean age of 52.2 years. All were White, and 99.3% were not Hispanic or Latino, reflective of the population in the regions in which the study was conducted (Central/Eastern Europe and Russia).

Table 12. Demographic Characteristics, Core Period, 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)
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)			
Mean (std)	51.2 (12.72)	53.2 (11.33)	52.2 (12.08)
Median	52.0	54.0	53.0
Age Groups, n (%)			
18-44	90 (29.8)	71 (23.5)	161 (26.7)
45-64	161 (53.3)	177 (58.6)	338 (56.0)
>=65	51 (16.9)	54 (17.9)	105 (17.4)
Baseline Weight (kg)			
Mean (std)	73.63 (14.110)	71.76 (13.518)	72.70 (13.837)
Median	72.40	70.60	71.75
Height (cm)			
Mean (std)	165.36 (8.104)	165.42 (8.138)	165.39 (8.114)
Median	165.00	165.00	165.00
Baseline BMI (kg/m^2)			
Mean (std)	26.91 (4.740)	26.22 (4.597)	26.56 (4.677)
Median	26.72	26.03	26.31

Source: Adapted from Table 17, Week 55 Clinical Study Report for Study FKS456-001

Baseline RA disease characteristics were generally similar between treatment arms, as shown in Table 13. The mean duration of RA disease was 93.1 months (approximately 7.75 years). Approximately 56% of subjects had received prior methotrexate, 45.6% other non-biologic DMARDs, 37% had received systemic corticosteroids, and 9% of subjects had previously received biologic treatments for RA. The mean DAS28-ESR at baseline was 6.27, corresponding to high disease activity. Subjects had an average of 10 swollen joints, 13 tender joints, and a HAQ-DI of 1.453 at baseline. The average CRP and ESR were 12.6 and 38.1, respectively.

In general, the baseline characteristics of subjects in Study FKS456-001 are representative of a RA patient population with moderately to severely active disease and were similar between the MSB11456 and EU-RoActemra treatment arms.

Table 13. Baseline Disease Characteristics, Core Period, ITT Analysis Set

Characteristics	MSB11456 (N=302)	EU-RoActemra (N=302)	Total (N=604)
RA Disease Duration (Months)			
Mean (std)	95.2 (79.91)	90.9 (83.47)	93.1 (81.67)
Median	73	66	69
Swollen Joint Counts (out of 28)	10.063 (4.499)	9.970 (4.339)	10.017 (4.416)
Tender Joint Counts (out of 28)	13.573 (5.224)	13.079 (5.275)	13.326 (5.251)
Patient Global Assessment (0-100 mm)	63.113 (18.476)	64.361 (19.121)	63.737 (18.796)
Physician Global Assessment (0-100 mm)	64.709 (14.090)	64.576 (13.915)	64.642 (13.991)
HAQ-DI (0-3 scale)	1.469 (0.581)	1.437 (0.593)	1.453 (0.587)
Acute Phase Reactants			
CRP	13.829 (26.788)	11.395 (15.599)	12.612 (21.935)
ESR	38.136 (13.595)	37.964 (12.979)	38.050 (13.280)
DAS28-ESR			
Mean (std)	6.28 (0.787)	6.26 (0.795)	6.27 (0.791)
Median	6.2	6.2	6.2
Prior Medications (n [%])			
Methotrexate	164 (54.3)	171 (56.6)	335 (55.5)
Systemic Corticosteroids	111 (36.8)	111 (36.8)	222 (36.8)
Biologics	28 (9.3)	26 (8.6)	54 (8.9)

Counts (percentages relative to N) or means (standard deviation) are presented.
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
Source: Adapted from Tables 18, 19, 20 and 14.1.5.2.1 of the Week 55 Clinical Study Report and the updated ADEFF dataset submitted with the Week 55 Clinical Study Report for Study FKS456-001

Concomitant Medications

Use of concomitant medications for RA was balanced across the treatment arms. During the Core Period, 100% of subjects in both treatment arms received methotrexate, consistent with the protocol requirement, and the proportions of subjects treated with systemic corticosteroids were generally balanced between treatment arms (MSB11456: 53.3%; EU-RoActemra: 57.6%). In the Extended Period, from Weeks 24 to 55, the majority of subjects across treatment arms continued methotrexate treatment (MSB11456: 97.5%; EU-RoActemra: 98.5%; EU-RoActemra/MSB11456: 98.6%), and concomitant corticosteroid use remained generally balanced by treatment arm (MSB11456: 52.1%; EU-RoActemra: 60.4%; EU-RoActemra/MSB11456: 50.4%). A single subject who continued MSB11456 in the Extended Period received chloroquine and sulfasalazine, and 1 subject who continued on EU-RoActemra was treated with leflunomide.

No subjects received intra-articular steroids or used biologic agents for RA, other than IMP, in either treatment period.

Analysis of Primary Clinical Endpoint(s)

The primary clinical endpoint was DAS28-ESR change from baseline at Week 24. The primary analysis was based on the ITT Analysis Set using all observed data for the primary clinical endpoint and used multiple imputation to address missing data. Using the primary analysis method, the statistical reviewer obtained a 90% confidence interval (CI) for the difference of means between the MSB11456 group and EU-RoActemra group of (-0.16, 0.18) which is fully included within the predefined similarity interval of [-0.6, 0.5] (Table 14). The statistical reviewer also obtained a 95% CI of (-0.19, 0.22) which is fully included within the similarity interval of [-0.6, 0.6] which was predefined by the Applicant for the EMA.

In addition to the primary analysis of DAS28-ESR change from baseline at Week 24, the following supportive/sensitivity analyses were also conducted, and the results are included in Table 14.

- Analysis like the primary analysis but based on the PP Analysis Set using all observed efficacy data for the primary clinical endpoint with no imputation of missing values.
- Analysis based on the ITT Analysis Set using an approach like the primary analysis except measurements that occurred after selected intercurrent events (IMP discontinuation or interruption prior to Week 24 due to lack of efficacy or adverse event) were not used but instead were multiply imputed using an approach representative of a hypothetical scenario where the subject's DAS28-ESR returned to baseline levels immediately after the intercurrent event. Other missing values were multiply imputed using an approach like the approach used for the primary analysis.
- Analysis based on the ITT Analysis Set using an approach like the primary analysis except measurements that occurred after selected intercurrent events (IMP discontinuation or interruption prior to Week 24, use of prohibited medication or change in permitted medication [other than methotrexate] with potential to impact Week 24 efficacy assessments) were not used but instead were multiply imputed using an approach representative of a hypothetical scenario where the subject had continued to follow the protocol.
- A sensitivity analysis was conducted based on the ITT Analysis Set using all observed data with no imputation of missing values.

For each of the supportive/sensitivity analyses, the 90% and 95% CIs for the difference of means between the MSB11456 group and EU-RoActemra group are contained in the predefined similarity intervals of [-0.6, 0.5] and [-0.6, 0.6], respectively.
Therefore, the statistical reviewer concluded that the primary endpoint analysis results including the primary, supportive, and sensitivity analyses show no meaningful differences in efficacy between MSB11456 and EU-RoActemra.

Table 14. Statistical Analysis Results for Primary Endpoint DAS28-ESR Change from Baseline at Week 24

Analysis Set: Analysis Method	MSB11456			EU-RoActemra			Difference
	N	N_1	LS Mean (SE) 95% CI	N	N_1	LS Mean (SE) 95% CI	LS Mean (SE) 90% CI 95% CI
ITT: All observed efficacy data using MI for missing values	302	25*	-3.53 (0.106) (-3.74, -3.32)	302	17*	-3.54 (0.106) (-3.75, -3.33)	0.01 (0.104) (-0.16. 0.18) (-0.19, 0.22)
PP: All observed efficacy data with no imputation of missing values	247	1	-3.71 (0.102) (-3.91, -3.51)	250	2	-3.69 (0.102) (-3.89, -3.49)	-0.02 (0.103) (-0.19, 0.15) (-0.23, 0.18)
ITT: Hypothetical Return-to-Baseline	302	69*	-3.06 (0.154) (-3.36, -2.76)	302	63*	-3.16 (0.154) (-3.46, -2.86)	0.10 (0.154) (-0.15, 0.35) (-0.20, 0.40)
ITT: Hypothetical Continuing as Per Protocol	302	102*	-3.61 (0.104) (-3.81, -3.40)	302	99*	-3.68 (0.105) (-3.89, -3.48)	0.07 (0.107) (-0.10, 0.25) (-0.14, 0.28)
ITT: All observed efficacy data with no imputation of missing values	302	25	-3.57 (0.107) (-3.78, -3.36)	302	17	-3.59 (0.107) (-3.80, -3.38)	0.02 (0.105) (-0.16, 0.19) (-0.19, 0.22)

N = number of subjects in the analysis set
N_1 = number of imputed values or number of missing values
*Multiple imputation
Source: Statistical Reviewer

Potential Effects of Missing Data

For the primary clinical endpoint, DAS28-ESR change from baseline at Week 24, the primary analysis was based on the ITT Analysis Set and used all observed data. In the ITT Analysis Set, there were 25 and 17 missing values of DAS28-ESR change from baseline at Week 24 in the MSB11456 and EU-RoActemra groups, respectively, and multiple imputation was used to address missing data under a missing at random (MAR) assumption. The imputation modeling incorporated DAS28-ESR data from baseline, and Weeks 2, 4, 8, 12, and 16 to enhance the plausibility of the MAR assumption. Analyses of the endpoint DAS28-ESR change from baseline at Week 12 were also conducted, where there were 20 and 10 missing values of this Week 12 endpoint in the MSB11456 and EU-RoActemra groups, respectively. These results (Table 14) supported the conclusions based primary efficacy endpoint.

To explore the sensitivity of results to various missing not at random situations, tipping point analysis was conducted. For the endpoint DAS28-ESR change from baseline at Week 24, the tipping point analysis utilized a δ-based multiple imputation method (Cro, 2020). The tipping point analysis used shift parameters δ_1 and δ_2 for adjustment of

imputed values in the MSB11456 and EU-RoActemra groups, respectively. Combinations of shift parameters δ_1 and δ_2 ranging over {-3, -2, -1, 0, 1, 2, 3} were considered; these combinations of shift parameters were prespecified in the Statistical Analysis Plan for this tipping point analysis.

The statistical reviewer's tipping point analysis results for the 90% CI based on the prespecified similarity margin of [-0.6, 0.5] are shown in Table 15. In this analysis, out of the $7 \times 7 = 49$ different combinations of δ_1 and δ_2 considered, two tipping points were identified corresponding to the $(\delta_1 = 3, \delta_2 = -3)$ and $(\delta_1 = 3, \delta_2 = -2)$ scenarios where the 90% CI is not contained in the similarity margin of [-0.6, 0.5]. The statistical reviewer noted that the tipping point $(\delta_1 = 3, \delta_2 = -2)$ was not identified in the Applicant's corresponding tipping point analysis. The Applicant appears to have rounded the 90% CI to one decimal place and this rounded CI satisfied the similarity margin, but the CI does not satisfy the margin if not rounded. The statistical reviewer's tipping point analysis results for the 95% CI based on the similarity margin of [-0.6, 0.6] are shown in Table 16. In this analysis, out of the $7 \times 7 = 49$ different combinations of δ_1 and δ_2 considered, one tipping point was identified corresponding to the scenario $(\delta_1 = 3, \delta_2 = -3)$. The tipping point $(\delta_1 = 3, \delta_2 = -3)$ was not identified in the Applicant's corresponding tipping point analysis due to the Applicant's rounding the 95% CI to one decimal place. In conclusion, the tipping point analysis for DAS28-ESR change from baseline at Week 24 supports the robustness of the conclusions of the primary analysis to plausible departures from the missing at random assumption.

For the endpoint ACR20 response at Week 24 there were 24 and 15 missing values in the ITT Analysis Set in the MSB11456 and EU-RoActemra groups, respectively. A tipping point analysis was conducted where the allocation of responders was varied over $\{0,1, \ldots, 24\}$ and $\{0,1, \ldots, 15\}$ for the 24 and 15 subjects with missing data in the MSB11456 and EU-RoActemra groups, respectively. This results in a total of $25 \times 16 = 400$ scenarios. The results of this tipping point analysis based on the 95% stratified Newcombe CI (Yan, 2010) and margin of [-15%,15%] are shown in Figure 14. In these results all scenarios yield the 95% CI contained in the margin [-15%,15%] and therefore no tipping points were identified. The tipping point analysis results may depend on allocation of responders/nonresponders with respect to the stratification variable (previous exposure to biologic treatment for rheumatoid arthritis). This statistical reviewer also conducted a tipping point analysis using the unstratified Newcombe CI (Newcombe, 1998). The results of this tipping point analysis based on the 95% unstratified Newcombe CI and margin of [-15%,15%] are shown in Figure 15. In these results all scenarios yield the 95% CI contained in the margin [-15%,15%] and therefore no tipping points were identified. In conclusion, the tipping point analysis for ACR20 response at Week 24 demonstrate robustness of the conclusions of the key secondary analysis to departures from the missing at random assumption.

Table 15. Tipping Point Analysis Based on DAS28-ESR Change from Baseline at Week 24 Using 90% CI and Similarity Margin of [-0.6, 0.5], ITT Analysis Set

δ_1:Shift for MSB11456	δ_2:Shift for EU-RoActemra						
	-3	-2	-1	0	1	2	3
-3	-0.04 (0.106) (-0.22, 0.13)	-0.07 (0.105) (-0.25, 0.10)	-0.12 (0.105) (-0.29, 0.05)	-0.17 (0.106) (-0.35, 0.00)	-0.23 (0.108) (-0.40, -0.05)	-0.28 (0.111) (-0.47, -0.10)	-0.34 (0.116) (-0.53, -0.15)
-2	-0.00 (0.105) (-0.17, 0.17)	-0.03 (0.104) (-0.20, 0.14)	-0.08 (0.104) (-0.25, 0.09)	-0.13 (0.104) (-0.30, 0.04)	-0.19 (0.107) (-0.36, -0.01)	-0.24 (0.110) (-0.42, -0.06)	-0.30 (0.115) (-0.49, -0.11)
-1	0.06 (0.104) (-0.11, 0.23)	0.03 (0.103) (-0.14, 0.20)	-0.01 (0.103) (-0.18, 0.15)	-0.07 (0.103) (-0.24, 0.10)	-0.12 (0.105) (-0.30, 0.05)	-0.18 (0.109) (-0.36, 0.00)	-0.24 (0.114) (-0.42, -0.05)
0	0.14 (0.104) (-0.03, 0.31)	0.11 (0.103) (-0.06, 0.28)	0.06 (0.103) (-0.11, 0.23)	0.01 (0.104) (-0.16, 0.18)	-0.05 (0.106) (-0.22, 0.13)	-0.10 (0.109) (-0.28, 0.08)	-0.16 (0.115) (-0.35, 0.03)
1	0.22 (0.107) (0.04, 0.39)	0.19 (0.106) (0.01, 0.36)	0.14 (0.106) (-0.03, 0.32)	0.09 (0.106) (-0.09, 0.26)	0.03 (0.108) (-0.14, 0.21)	-0.02 (0.111) (-0.21, 0.16)	-0.08 (0.116) (-0.27, 0.11)
2	0.30 (0.111) (0.12, 0.48)	0.27 (0.110) (0.09, 0.45)	0.22 (0.110) (0.04, 0.41)	0.17 (0.110) (-0.01, 0.35)	0.12 (0.112) (-0.07, 0.30)	0.06 (0.115) (-0.13, 0.25)	0.01 (0.120) (-0.19, 0.20)
3	0.38 (0.117) (0.19, 0.58)	0.35 (0.116) (0.16, 0.54)	0.31 (0.116) (0.12, 0.50)*	0.26 (0.117) (0.06, 0.45)	0.20 (0.118) (0.01, 0.40)	0.14 (0.122) (-0.05, 0.34)	0.09 (0.126) (-0.12, 0.30)

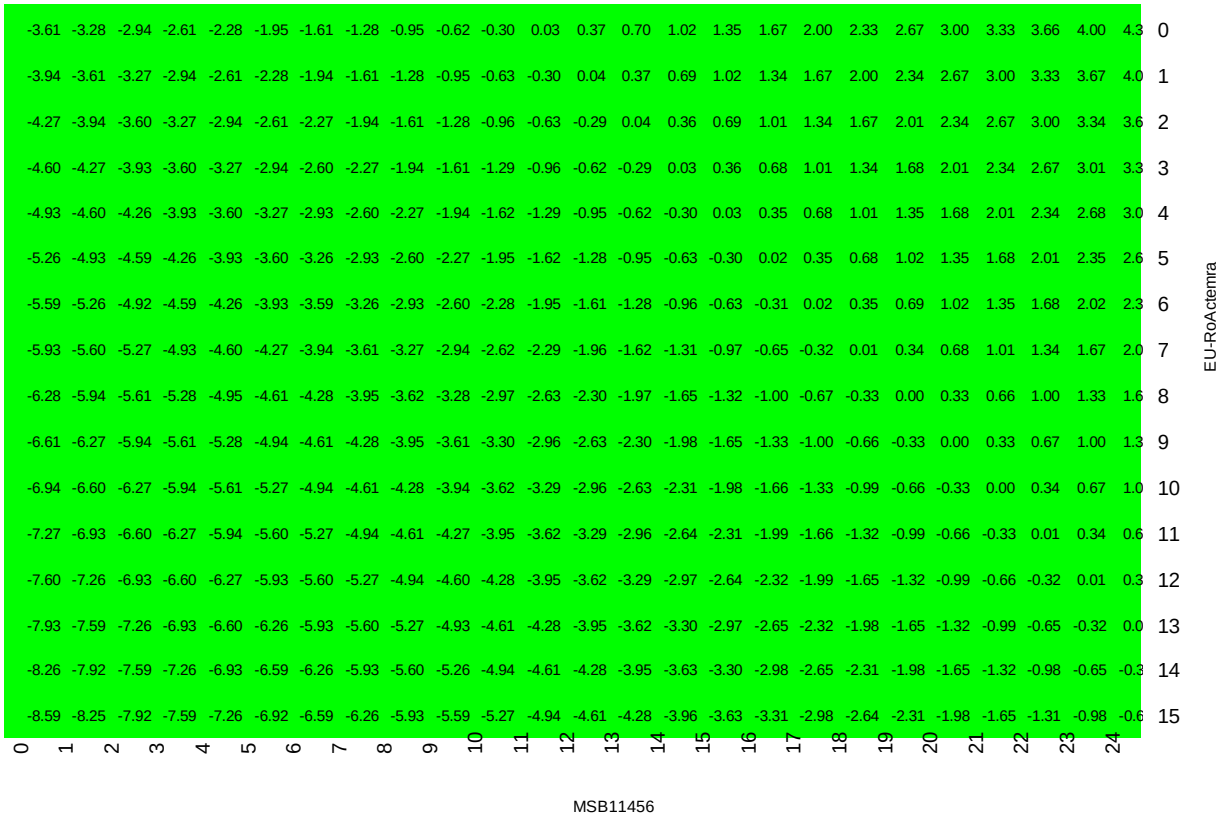
*The 90% CI for $\delta_1 = 3$, $\delta_2 = -1$ scenario rounded to three decimal places is (0.117, 0.499).
Note: Green shaded cells correspond combinations of shift parameters yielding a 90% CI that is contained in the similarity margin of [-0.6, 0.5].
Source: Statistical Reviewer

Table 16. Tipping Point Analysis Based on DAS28-ESR Change from Baseline at Week 24 Using 95% CI and Similarity Margin of [-0.6, 0.6], ITT Analysis Set

δ_1:Shift for MSB11456	δ_2:Shift for EU-RoActemra						
	-3	-2	-1	0	1	2	3
-3	-0.04 (0.106) (-0.25, 0.17)	-0.07 (0.105) (-0.28, 0.13)	-0.12 (0.105) (-0.32, 0.09)	-0.17 (0.106) (-0.38, 0.03)	-0.23 (0.108) (-0.44, -0.02)	-0.28 (0.111) (-0.50, -0.07)	-0.34 (0.116) (-0.57, -0.11)
-2	-0.00 (0.105) (-0.21, 0.20)	-0.03 (0.104) (-0.24, 0.17)	-0.08 (0.104) (-0.28, 0.13)	-0.13 (0.104) (-0.33, 0.07)	-0.19 (0.107) (-0.40, 0.02)	-0.24 (0.110) (-0.46, -0.03)	-0.30 (0.115) (-0.52, -0.07)
-1	0.06 (0.104) (-0.14, 0.27)	0.03 (0.103) (-0.17, 0.23)	-0.01 (0.103) (-0.22, 0.19)	-0.07 (0.103) (-0.27, 0.14)	-0.12 (0.105) (-0.33, 0.08)	-0.18 (0.109) (-0.39, 0.03)	-0.24 (0.114) (-0.46, -0.01)
0	0.14 (0.104) (-0.07, 0.34)	0.11 (0.103) (-0.10, 0.31)	0.06 (0.103) (-0.14, 0.26)	0.01 (0.104) (-0.20, 0.21)	-0.05 (0.106) (-0.26, 0.16)	-0.10 (0.109) (-0.32, 0.11)	-0.16 (0.115) (-0.39, 0.06)
1	0.22 (0.107) (0.01, 0.43)	0.19 (0.106) (-0.02, 0.39)	0.14 (0.106) (-0.06, 0.35)	0.09 (0.106) (-0.12, 0.30)	0.03 (0.108) (-0.18, 0.24)	-0.02 (0.111) (-0.24, 0.20)	-0.08 (0.116) (-0.31, 0.15)
2	0.30 (0.111) (0.08, 0.52)	0.27 (0.110) (0.05, 0.48)	0.22 (0.110) (0.01, 0.44)	0.17 (0.110) (-0.04, 0.39)	0.12 (0.112) (-0.10, 0.34)	0.06 (0.115) (-0.16, 0.29)	0.01 (0.120) (-0.23, 0.24)
3	0.38 (0.117) (0.16, 0.61)	0.35 (0.116) (0.12, 0.58)	0.31 (0.116) (0.08, 0.54)	0.26 (0.117) (0.03, 0.48)	0.20 (0.118) (-0.03, 0.48)	0.14 (0.122) (-0.09, 0.38)	0.09 (0.126) (-0.16, 0.34)

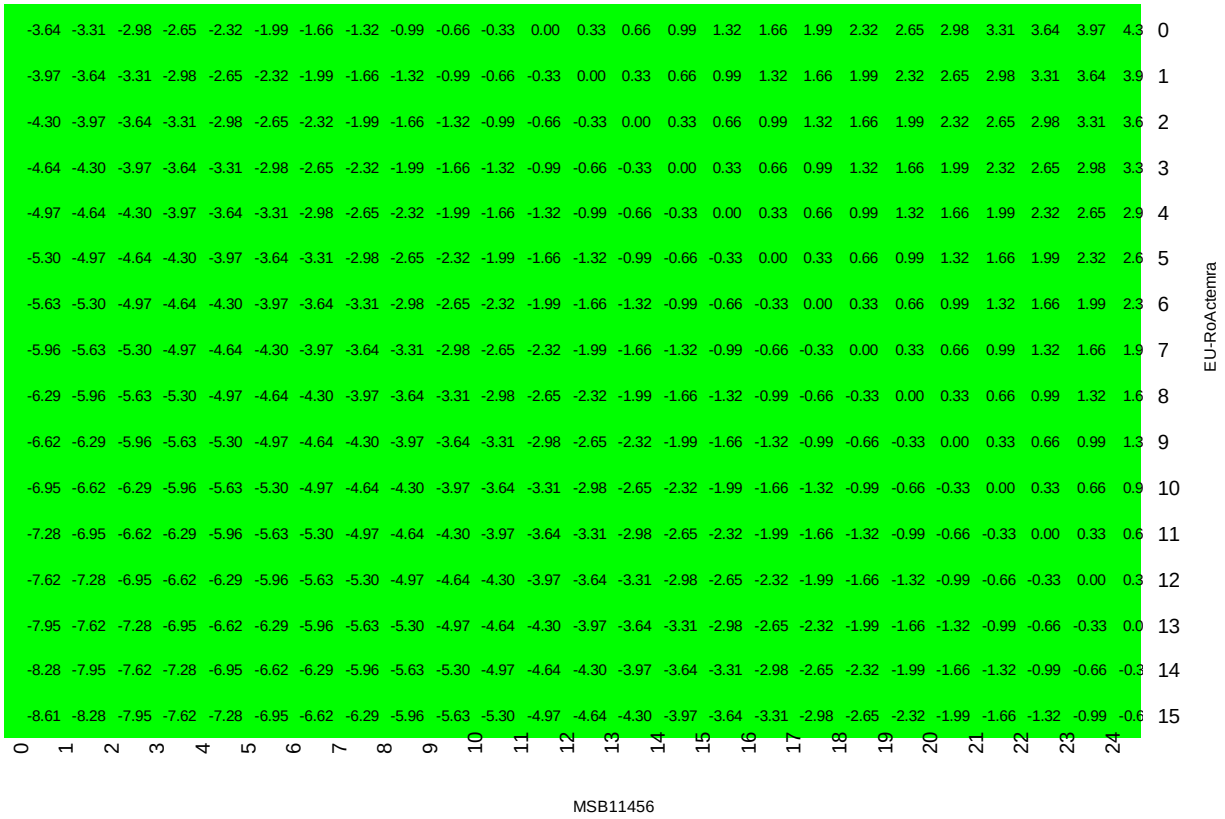
Note: Green shaded cells correspond combinations of shift parameters yielding a 95% CI that is contained in the similarity margin of [-0.6, 0.6].
Source: Statistical Reviewer

Figure 14. Tipping Point Analysis Based on ACR20 Response at Week 24 Using 95% CI and Similarity Margin of [-15%, 15%], ITT Analysis Set Using the Stratified Newcombe CI



Notes: (1) x-axis and y-axis represent number of ACR20 Week 24 responders allocated among subjects with missing data in MSB11456 and EU-RoActemra groups, respectively. (2) The number in each cell represents the estimated difference (weighted) in ACR20 response rates between the MSB11456 group and EU-RoActemra group. (3) Green shaded cells correspond to scenarios where the 95% CI is contained in the similarity margin of [-15%, 15%] (all scenarios in this analysis yield 95% CI contained in the similarity margin of [-15%, 15%]).
Source: Statistical Reviewer

Figure 15. Tipping Point Analysis Based on ACR20 Response at Week 24 Using 95% CI and Similarity Margin of [-15%, 15%], ITT Analysis Set Using the Unstratified Newcombe CI



Note: (1) x-axis and y-axis represent number of ACR20 Week 24 responders allocated among subjects with missing data in MSB11456 and EU-RoActemra groups, respectively. (2) The number in each cell represents the estimated difference (unweighted) in ACR20 response rates between the MSB11456 group and EU-RoActemra group. (3) Green shaded cells correspond to scenarios where the 95% CI is contained in the similarity margin of [-15%, 15%] (all scenarios in this analysis yield 95% CI contained in the similarity margin of [-15%, 15%]).
Source: Statistical Reviewer

Analysis of Key Secondary Clinical Endpoint(s)

The key secondary clinical endpoint was ACR20 response at Week 24. The key secondary analysis was based on the ITT Analysis Set using all observed data for the key secondary clinical endpoint and used LOCF to impute missing data. Using the key secondary analysis method, the statistical reviewer obtained a 95% CI for the difference in ACR20 response rates between the MSB11456 group and EU-RoActemra group of (-9.97%, 2.11%) (using the Newcombe CI to adjust for the stratification factor previous exposure to biological treatment for rheumatoid arthritis [yes/no]) which is fully included within the predefined similarity interval of [-15%, 15%] (Table 17).

In addition to the key secondary analysis of ACR20 response rate at Week 24, the following supportive/sensitivity analyses were also conducted.

- Analysis like the key secondary analysis but based on the PP Analysis Set and using all observed efficacy data for the key secondary clinical endpoint with no imputation of missing values.
- Analysis based on the ITT Analysis Set using an approach like the key secondary analysis except measurements that occurred after selected intercurrent events (IMP discontinuation or interruption prior to Week 24 due to lack of efficacy or an adverse event) were not used but instead were imputed as ACR20 nonresponders. Other missing values were imputed using LOCF.
- A sensitivity analysis was conducted based on the ITT Analysis Set using all observed efficacy data for the key secondary endpoint with no imputation of missing values.
- Another sensitivity analysis was conducted based on the ITT Analysis Set using all observed data with multiple imputation to address missing data.

For each of the supportive/sensitivity analyses of the key secondary endpoint, the 95% CI for difference in ACR20 response rates between the MSB11456 group and EU-RoActemra group is contained in the predefined similarity interval of [-15%, 15%]. Therefore, the statistical reviewer concluded that the analysis results based on the key secondary endpoint, including the key secondary analysis, and supportive/sensitivity analyses support the conclusion of the primary clinical endpoint analyses of no meaningful differences in efficacy between MSB11456 and EU-RoActemra.

Table 17. Statistical Analysis Results for Key Secondary Endpoint ACR20 Response at Week 24

Analysis Set: Analysis Method	MSB11456			EU-RoActemra			Difference in % Response Rate
	N	N_1	Responder n (%)	N	N_1	Responder n (%)	Estimate 95% CI
ITT: All observed efficacy data using LOCF for missing values	302	24	244 (80.79%)	302	15	256 (84.77%)	-3.94% (-9.97%, 2.11%)
PP: All observed efficacy data with no imputation of missing values	247	0	220 (89.07%)	250	0	221 (88.40%)	0.67% (-5.00%, 6.33%)
ITT: Hypothetical nonresponder	302	68	211 (69.87%)	302	61	217 (71.85%)	-2.02% (-9.24%, 5.22%)
ITT: All observed efficacy data with no imputation of missing values	302	24	238 (85.61%)	302	15	249 (86.76%)	-1.13% (-6.90%, 4.60%)
ITT: All observed efficacy data using MI for missing values	302	24*	---	302	15*	---	-1.21% (-7.02%, 4.60%)**

N = number of subjects in the analysis set
N_1 = number of imputed values or number of missing values
*Multiple imputation
**This 95% CI differs from the 95% CI of (-7.06%, 4.65%) obtained by the Applicant based on the ITT Analysis Set using MI for missing values. The Applicant used a nonstandard method to calculate standard errors from each of the multiply imputed datasets from the stratified Newcombe CI (Yan,2010). The statistical reviewer used the standard error of the Mantel-Haenszel estimate as reported by SAS PROC FREQ to analyze each multiply imputed dataset, and then applied multiple imputation combination formulas to obtain the 95% CI.
Source: Statistical Reviewer

Additional Analyses

The following additional supportive analyses were performed based on the supportive clinical endpoint DAS28-ESR change from baseline at Week 12, and the results of these analyses are included in Table 18.

- Analysis based on the ITT Analysis Set using all observed data for this supportive clinical endpoint and using multiple imputation to address missing data.
- Analysis based on the PP Analysis Set using all observed efficacy data for this supportive clinical endpoint with no imputation of missing data.
- Analysis based on the ITT Analysis Set where measurements that occurred after selected intercurrent events (IMP discontinuation or interruption prior to Week 12, use of prohibited medication or change in permitted medication [other than methotrexate] with potential to impact Week 12 efficacy assessments) were not used

but instead were multiply imputed using an approach representative of a hypothetical scenario where the subject had continued to follow the protocol.

- Analysis based on the ITT Analysis Set using all observed data with no imputation of missing values.

The analysis results of DAS28-ESR change from baseline at Week 12 (Table 18) are similar to the corresponding analysis results of DAS28-ESR change from baseline at Week 24 (Table 14). Of note, the 90% and 95% CIs for the difference of means DAS28-ESR change from baseline at Week 12 between the MSB11456 group and EU-RoActemra groups are contained in the similarity intervals [-0.6, 0.5] and [-0.6, 0.6], respectively, which were prespecified for the primary endpoint analyses. Therefore, the statistical reviewer concluded that these supportive clinical endpoint analyses support a finding of no meaningful differences in efficacy between MSB11456 and EU-RoActemra.

Table 18. Statistical Analysis Results for Supportive Endpoint DAS28-ESR Change from Baseline at Week 12

Analysis Set: Analysis Method	MSB11456			EU-RoActemra			Difference
	N	N_1	LS Mean (SE) 95% CI	N	N_1	LS Mean (SE) 95% CI	LS Mean (SE) 90% CI 95% CI
ITT: All observed efficacy data using MI for missing values	302	20*	-3.13 (0.104) (-3.33, -2.92)	302	10*	-3.12 (0.104) (-3.32, -2.92)	-0.01 (0.103) (-0.18, 0.16) (-0.21, 0.19)
PP: All observed efficacy data with no imputation of missing values	261	1	-3.16 (0.106) (-3.37, -2.96)	267	0	-3.13 (0.107) (-3.34, -2.92)	-0.03 (0.108) (-0.21, 0.15) (-0.24, 0.18)
ITT: Hypothetical Continuing as Per Protocol	302	74*	-3.15 (0.106) (-3.36, -2.94)	302	60*	-3.16 (0.104) (-3.36, -2.95)	0.01 (0.107) (-0.17, 0.18) (-0.20, 0.22)
ITT: All observed efficacy data with no imputation of missing values	302	20	-3.16 (0.105) (-3.37, -2.96)	302	10	-3.13 (0.105) (-3.33, -2.92)	-0.03 (0.104) (-0.21, 0.14) (-0.24, 0.17)

N = number of subjects in the analysis set.
N_1 = number of imputed values or number of missing values.
*Multiple imputation.
Source: Statistical Reviewer

Subgroup Analyses

The statistical reviewer performed subgroup analyses using DAS28-ESR change from baseline at Week 24 based on sex, age, and the following subgroups which were prespecified in the Statistical Analysis Plan.

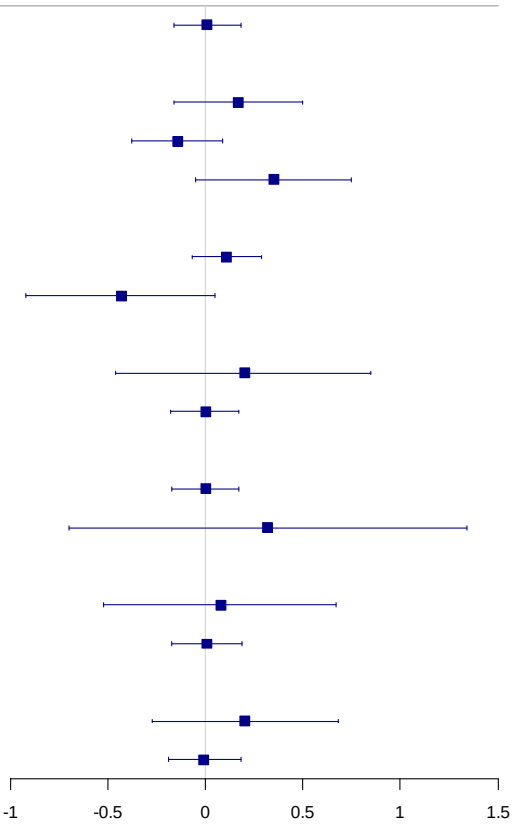
- Previous exposure to biologic treatment for RA [yes/no].

- ADA positive/ADA negative.
- Neutralizing antibody (NAb) positive/NAb negative.
- Non COVID-19 vaccinated/COVID-19 vaccinated prior to Week 24.

The statistical reviewer's results are shown in Figure 16. These analyses are descriptive in nature. There were no notable efficacy trends favoring MSB11456 or EU-RoActemra in these subgroup analyses except age and gender. Descriptively speaking, the age group 45-64 shows a negative point estimate whereas the other two age groups 18-44 and >=65 show positive point estimates. Similarly, the male group shows a negative point estimate whereas the female group shows a positive estimate. Note that many subgroups have small sample sizes, and observations should be considered as exploratory.

Figure 16. Subgroup Analysis of DAS28-ESR Change from Baseline at Week 24

Subgroups	Estimate (90% CI)
Overall [302, 302]	0.01 (-0.16, 0.18)
Age Group	
18-44 [90, 71]	0.17 (-0.16, 0.50)
45-64 [161, 177]	-0.14 (-0.38, 0.09)
>=65 [51, 54]	0.35 (-0.05, 0.75)
Sex	
F [250, 248]	0.11 (-0.07, 0.29)
M [52, 54]	-0.43 (-0.92, 0.05)
Previous Exposure	
Yes [28, 26]	0.20 (-0.46, 0.85)
No [274, 276]	0.00 (-0.18, 0.17)
Antidrug Antibody Incidence	
Yes [287, 290]	0.00 (-0.17, 0.17)
No [15, 12]	0.32 (-0.70, 1.34)
Neutralizing Antibody	
Yes [25, 34]	0.08 (-0.52, 0.67)
No [277, 268]	0.01 (-0.17, 0.19)
COVID-19 Vaccine	
Yes [38, 30]	0.20 (-0.27, 0.68)
No [264, 272]	-0.01 (-0.19, 0.18)



Note: (1) The numbers $[N_1, N_2]$ in the column labeled "Subgroups" represent the number of subjects in the MSB11456 and EU-RoActemra arms, respectively, for the subgroup. (2) In the "Subgroups" column "Overall" represents the primary analysis results shown in Table 14. (3) The "Estimate" column provides the estimate of the difference of means between the MSB11456 arm and EU-RoActemra arm and corresponding 90% CI.
Source: Statistical Reviewer

Statistical Issues

There were no major statistical issues in this study.

Conclusions and Recommendations

The conclusions from the statistical reviewer's analyses agreed with those of the Applicant. For the primary analysis the statistical reviewer obtained a 90% confidence interval for the difference of mean change from baseline of DAS28-ESR at Week 24 between the MSB11456 and EU-RoActemra groups of (-0.16, 0.18), which is contained in the prespecified similarity margin of [-0.6, 0.5]. The key secondary analysis, as well as supportive and sensitivity analyses of DAS28-ESR change from baseline at Week 24,

ACR response rate at Week 24, and DAS28-ESR change from baseline at Week 12, as discussed in this review, further support the conclusion of similar efficacy for MSB11456 and EU-RoActemra. Together, the efficacy based on the primary and key secondary endpoints support a demonstration of no clinically meaningful efficacy differences between MSB11456 and US-Actemra, as the Applicant provided adequate data to establish the scientific bridge between MSB11456, US-Actemra, and EU-RoActemra to justify the relevance of data generated with EU-RoActemra to the assessment of biosimilarity.

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6.3. Review of Safety Data

6.3.1. Methods

Clinical Studies Used to Evaluate Safety

The Applicant provided safety data from the 4 clinical studies presented in Table 2 and summarized below.

The safety database for the current submission includes data from a total of 1517 subjects from the four clinical studies including 913 healthy subjects (MS200740001, FSK456-002, FSK456-003) and 604 subjects with RA (FKS456-001) who received at least 1 dose of MSB11456, EU-RoActemra, or US-Actemra. Of these, 331 healthy subjects received SC MSB11456, 62 healthy subjects received IV MSB11456, and 441 subjects with RA received MSB11456. The size of the safety database is adequate to provide a reliable descriptive comparison between the products.

The primary safety data are provided from the comparative clinical study FKS456-001, a 52 week, randomized, double-blind, multiple-dose, parallel-group, two-arm study in subjects with moderately to severely active rheumatoid arthritis with an inadequate response to methotrexate therapy treated with SC MSB11456 or SC EU-RoActemra. At Week 24, a subset of subjects originally randomized to EU-RoActemra were rerandomized (1:1) to continue EU-RoActemra or transition to MSB11456 to assess for potential immune-related safety issues after transitioning from EU-RoActemra to MSB11456 (EU-RoActemra/MSB11456), compared to continuing on EU-RoActemra. The safety population includes 604 subjects who received at least 1 dose of IMP; 302 subjects who received MSB11456 during the Core Period (up to Week 24), and 405 subjects who received MSB11456 during the Extended Period (Weeks 24-52).

As noted in Section 6.2.1, the Applicant included updates to the Core Period data in the Week 55 CSR and supporting datasets to reflect additional information received after the initial database lock for the Week 30 CSR. There were small changes to the number and type of adverse events reported accompanied by detailed explanations for a limited number of subjects. These changes to the safety data did not impact the safety conclusions. The primary safety assessment presented in this review was based on the Week 55 CSR and the supporting datasets.

The primary safety assessment was further supported by the review of safety data from 3 comparative single-dose PK studies in healthy subjects (Studies MS200740-0001, FKS456-002, and FKS456-003).

The numbers of subjects who received at least one dose of study drug are presented by study and treatment arm below:

Healthy Subjects: In Study MS200740-0001, 685 subjects received a single dose of 162 mg/0.9 mL IMP administered SC with 48 days of post-dosing safety follow up:

- MSB11456: 231 subjects
- US-Actemra: 229 subjects
- EU-RoActemra: 225 subjects

In Study FKS456-002, 128 subjects received a single dose of 8 mg/kg IMP administered IV followed by 48 days of post-dosing safety follow up:

- MSB11456: 62 subjects
- US-Actemra: 66 subjects

In Study FKS456-003, 100 subjects received at least 1 dose of SC administered MSB11456 via AI or PFS. Among these subjects, 91 received 2 doses separated by 7 weeks. Each exposure was followed by 7 weeks (i.e. 42 days) of post-dosing safety follow up.

- MSB11456 PFS: 94 subjects
- MSB11456 AI: 97 subjects

Subjects with RA: In FKS456-001, 604 subjects with RA received at least one dose of 162 mg/0.9 mL IMP administered SC weekly for up to 52 weeks with subsequent safety follow up for up to 12 weeks after the last dose. The number of subjects by treatment received for both the 24-week Core Period and the 28-week blinded Extended Period were as follows:

- MSB11456: 302 subjects in the Core Period and 266 subjects in the Extended Period
- EU-RoActemra: 302 subjects in the Core Period and 136 subjects in the Extended Period
- EU-RoActemra followed by a Week 24 transition to MSB11456: 139 subjects in the Extended Period

Table 19 and Table 20, respectively, present the mean duration of exposure, mean total number of doses received, and compliance for the Core and Extended Periods.

Table 19. Exposure in the Core Period, Safety Population

	MSB11456 N=302	EU-RoActemra N=302
Duration of Exposure (Weeks) Mean (SD)	22.25 (5.153)	22.91 (3.921)
Doses Administered Mean (SD)	21.6 (5.20)	22.2 (4.01)
Compliance Mean (SD)	90.01 (21.647)	92.66 (16.720)

Source: Table 14.3.1.2.1, Week 55 Clinical Study Report for Study FKS456-001

Table 20. Exposure in the Extended Period, Weeks 24 to 55, Safety Population

	MSB11456 N=266	EU-RoActemra N=136	EU-RoActemra/ MSB11456 N=139
Duration of Exposure (Weeks) Mean (SD)	26.06 (6.355)	26.62 (5.183)	25.46 (6.922)
Doses Administered Mean (SD)	25.1 (6.48)	25.7 (5.73)	24.8 (6.97)
Compliance Mean (SD)	90.08 (22.503)	92.52 (18.953)	88.62 (24.906)

Source: Table 14.3.1.2.2, Week 55 Clinical Study Report for Study FKS456-001

The mean duration of exposure and the mean number of doses administered were similar across treatment arms in both the Core and Extended Periods. Mean compliance (defined as the mean proportion of actual versus planned injections) was also similar across treatment arms in both treatment periods.

Categorization of Adverse Events

Adverse events and serious adverse events were defined according to standard ICH definitions. For the comparative clinical study FKS-456-001, all confirmed COVID-19 cases were considered as 'otherwise medically important' and reported as SAEs.

Treatment-emergent adverse events (TEAEs) were defined as occurring or worsening (in severity or relationship to IMP) with an onset at the time of or following dosing time at Visit 2 (initial injection at Day 1). The intensity of AEs was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5. If no guidance was provided by the NCI-CTCAE, the investigator assessed the severity of AEs based on best medical judgment on the following 5-point scale: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening),

Grade 5 (death). Causality was assessed by the Investigator based on the following definitions:

Related:

- The AE followed a reasonable temporal sequence to IMP administration, and could not be reasonably explained by patient's clinical state or other factors
- The AE followed a reasonable temporal sequence to IMP administration, and it was a known reaction to the drug under study or a related chemical group or was predicted by known pharmacology

Not related: AE did not follow a reasonable sequence from IMP administration, or it could be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

AEs were coded based on the most current MedDRA versions at the time of database lock for each of the 4 clinical studies in the MSB11456 development program: version 22.1 for Study MS200740-0001, version 23.0 for Studies FKS456-002 and FKS456-003, and version 23.1 for Study FKS456-001.

For the comparative clinical study FKS456-001, adverse events of special interest (AESIs) were defined based on the known risks associated with U.S. Actemra and included the following:

- Serious infections, defined as those requiring administration of intravenous antibiotics
- Hypersensitivity and anaphylaxis, with hypersensitivity defined as an AE that occurred during or within 24 hours of an injection (excluding injection site reactions) and deemed related to treatment. Anaphylactic reactions were identified based on Sampson's criteria (Sampson, 2006). Hypersensitivity and anaphylaxis were analyzed using standard MedDRA queries (SMQs).
- Adverse events leading to the interruption of study treatment, permanent discontinuation of study treatment, or withdrawal from the study

For the comparative PK studies conducted in healthy subjects (Studies MS200740-0001, FKS456-002, and FKS456-003), serious infections and serious or severe hypersensitivity reactions were specified as AESIs. Additionally, Study MS200740-0001 evaluated injection site reactions considered related to study treatment by the Investigator as AESIs.

Safety Analyses

All subjects in the safety population, defined as all subjects randomized and treated with at least one dose of IMP, were included in the safety analyses. Because of inherent differences in study design and populations, the Applicant did not plan or perform any integrated (pooling) analysis of the AE data across the 4 clinical studies. This approach

is consistent with the discussion during the BPD Type 2 meeting on June 30, 2021 (see Section 2.1 for details).

TEAEs and TE-SAEs were summarized by System Organ Class (SOC) and preferred term (PT) according to MedDRA terminology with descriptive comparisons between MSB11456 and EU-RoActemra and, where applicable, US-Actemra.

6.3.2. Major Safety Results

Relevant Characteristics of the Population Evaluated for Safety

In Study FKS456-001, the relevant demographic and disease characteristics of the subject population were generally balanced between treatment arms (see Table 12 and Table 13), and consistent with the population of patients with RA eligible for treatment with tocilizumab.

For the healthy subjects in the 3 comparative PK studies (Studies MS200740-0001, FKS456-002, and FKS456-003), the baseline demographic characteristics were also generally balanced between treatment arms. In Study MS200740-0001, 52.2% of subjects were male, most subjects were white (74.0%) and not Hispanic (94.2%), and the mean age was 27 years (standard deviation 7.6 years). In Study FKS456-002, 68.8% of subjects were male, all were white and non-Hispanic, and the mean age was 34.1 years (standard deviation 9.31 years). In study FKS456-003, 62.0% of subjects were male, all were white and non-Hispanic, and the mean age was 34.4 years (standard deviation 9.84 years).

Other Product-Specific Safety Concerns

None.

Deaths

Four (4) deaths were reported in subjects treated with IMP during the MSB11456 clinical development program; all were reported in subjects with RA in Study FKS456-001. Two (2) of the deaths occurred in subjects who received EU-RoActemra during the Core Period: a 72 year-old male due to COVID-19 and a 58 year-old female due to an acute myocardial infarction. In the Extended Period, a 71 year-old female subject receiving EU-RoActemra experienced a fatal event of COVID-19 pneumonia, and a 69 year-old male subject who transitioned from EU-RoActemra to MSB11456 suffered a fatal myocardial infarction on Study Day 363. None of these deaths were determined to be related to IMP by either the Investigator or the Applicant. One additional death due to gastric ulcer perforation was reported prior to randomization.

Based on review of the submitted narratives, the 2 subjects who died of acute myocardial infarction had medical comorbidities that may have increased their cardiac risks. Aside from the underlying disease of RA, which is associated with increased cardiac risk, both subjects had hypertension, and 1 was a current smoker with hyperlipidemia. Given the multiple cardiac risk factors, the deaths were not likely to be related to study treatment. In addition, there was no imbalance in the number of deaths due to myocardial infarction.

No deaths were reported in the healthy subjects in the 3 PK studies (Studies MS200740-0001, FKS456-002, and FKS456-003).

Serious Adverse Events (SAEs)

Subjects with RA: In the Core Period, 9.3% and 9.9% of subjects in the MSB11456 and EU-RoActemra treatment arms, respectively, reported treatment-emergent SAEs (TE-SAEs) as presented in Table 21. TE-SAEs were most commonly reported in the Infections and Infestations SOC, and were generally balanced by arm (MSB11456: 7.0%, EU-RoActemra: 5.6%). By PT, COVID-19 was the most commonly reported TE-SAE, and was reported by similar proportions of subjects in each treatment arm (MSB11456 6.0%, EU-RoActemra 5.6%). As noted in Section 6.3.1, all confirmed COVID-19 cases during the study were defined as “serious” using the category “otherwise medically important,” triggering classification and management of these events as SAEs regardless of severity. Among subjects with COVID-19, the majority were mild or moderate in severity. Grade 3 events of COVID-19 were reported in 4 subjects in MSB11456 arm and in 5 subjects in EU-RoActemra. There were no Grade 4 events of COVID-19 and 1 subject in the EU-Actemra arm had a Grade 5 event (see above discussion of “Deaths”). Other TE-SAEs by SOC and PT were generally balanced by treatment arm. Spinal stenosis was reported in 2 subjects in the MSB11456 treatment arm, and all other TE-SAEs were singular by PT.

Table 21. TE-SAEs, Core Period, Safety Population

System Organ Class Preferred Term	MSB11456 N=302 n (%)	EU-RoActemra N=302 n (%)
Number of subjects with ≥ 1 TE-SAEs	**28 (9.3)**	**30 (9.9)**
Infections and Infestations	**21 (7.0)**	**17 (5.6)**
COVID-19	18 (6.0)	17 (5.6)
Abscess Limb	1 (0.3)	0
Asymptomatic COVID-19	1 (0.3)	0
Cellulitis	1 (0.3)	0
Musculoskeletal and Connective Tissue Disorders	**4 (1.3)**	**1 (0.3)**
Spinal Stenosis	2 (0.7)	0
Foot Deformity	1 (0.3)	0
Rheumatoid Arthritis	0	1 (0.3)
Spondyloarthropathy	1 (0.3)	0
Spondylolisthesis	1 (0.3)	0
Cardiac Disorders	**1 (0.3)**	**3 (1.0)**
Acute Myocardial Infarction	0	1 (0.3)
Atrioventricular Block Complete	1 (0.3)	0
Cardiogenic Shock	1 (0.3)	0
Coronary Artery Stenosis	0	1 (0.3)
Coronary Artery Thrombosis	0	1 (0.3)
Myocardial Infarction	1 (0.3)	0
Nervous System Disorders	**1 (0.3)**	**2 (0.7)**
Carotid Artery Disease	0	1 (0.3)
Ischaemic Stroke	0	1 (0.3)
Transient Ischaemic Attack	1 (0.3)	0
Blood and Lymphatic System Disorders	**0**	**2 (0.7)**
Iron Deficiency Anaemia	0	1 (0.3)
Neutropenia	0	1 (0.3)
Hepatobiliary Disorders	**0**	**2 (0.7)**
Autoimmune Hepatitis	0	1 (0.3)
Cholecystitis	0	1 (0.3)
Cholelithiasis	0	1 (0.3)
Hepatic Steatosis	0	1 (0.3)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**1 (0.3)**	**1 (0.3)**
Basal Cell Carcinoma	0	1 (0.3)
Follicular Thyroid Cancer	1 (0.3)	0
Injury, Poisoning and Procedural Complications	**0**	**1 (0.3)**
Wrist Fracture	0	1 (0.3)
Renal and Urinary Disorders	**1 (0.3)**	**0**
Cystitis Noninfective	1 (0.3)	0
Reproductive System and Breast Disorders	**0**	**1 (0.3)**
Ovarian Cyst	0	1 (0.3)
Vascular Disorders	**1 (0.3)**	**0**
Thrombophlebitis	1 (0.3)	0

Source: Adapted from Table 74, Week 55 Clinical Study Report for Study FKS456-001

Between Weeks 24 and 30 in the Extended Period, no increase in TE-SAEs was observed in subjects who underwent a single transition from EU-RoActemra to MSB11456, compared to those who continued treatment. No subjects in the EU-RoActemra/MSB11456 arm reported TE-SAEs, while a single subject who remained on EU-RoActemra reported a TE-SAE of COVID-19 and, in the MSB11456 arm, 3 (1.1%) subjects reported TE-SAEs of COVID-19, and 1 (0.4%) subject reported TE-SAEs of uterine leiomyoma and menorrhagia. No other TE-SAEs were reported.

Between Weeks 24 and 55 in the Extended Period, the TE-SAEs by SOC and PT remained generally balanced between the treatment arms and consistent with the types of TE-SAEs reported in the Core Period (Table 31). TE-SAEs were reported in 7.5%, 8.8%, and 7.2%, respectively, of subjects in the MSB11456, EU-RoActemra, and EU-RoActemra/MSB11456 arms. TE-SAEs were most frequently reported in the Infections and Infestations SOC (MSB11456: 6.8%; EU-RoActemra: 6.6%; EU-RoActemra/MSB11456: 4.3%). COVID-19 remained the most commonly reported TE-SAE, occurring in 6.8% of subjects in the MSB11456 arm, 5.1% of subjects in the EU-RoActemra arm, and in 3.6% of subjects in the EU-RoActemra/MSB11456 arm. All other TE-SAEs were singular events by PT.

Healthy Subjects: Across the 3 PK studies, small numbers of healthy subjects experienced SAEs, and no clustering by PT or SOC was observed.

In Study MS200740-0001, 5 healthy subjects treated with single doses of SC administered IMP reported SAEs. Singular events of appendicitis, spontaneous pneumothorax, and spontaneous abortion were reported in unique subjects who received MSB11456. Another subject treated with EU-RoActemra experienced an event of appendicitis. A single subject treated with US-Actemra experienced abdominal pain.

In Study FKS456-002, no SAEs were reported in the healthy subjects treated with single doses of IV administered IMP.

In Study FKS456-003, SAEs were reported in 2 healthy subjects including 1 PFS-treated subject with a SARS-CoV-2 test positive and 1 subject with an event of hypersensitivity with itching, urticaria, and erythema approximately 4.5 hours after receiving a SC administered dose of MSB11456 via AI in Period 2. The subject did not have respiratory symptoms, GI or urinary systems, and the event resolved within 2 hours after IV steroids and antihistamine treatment.

Treatment-Emergent Adverse Events (TEAEs)

Subjects with RA: In the Core Period, 65.9% of subjects in the MSB11456 arm and 62.9% of subjects in the EU-RoActemra arm reported TEAEs, generally balanced between treatment arms by SOC and PT, as shown in Table 22.

TEAEs in the Investigations SOC (MSB11456: 21.5%; EU-RoActemra: 25.8%) and the Infections and Infestations SOC (MSB11456: 18.5%; EU-RoActemra: 17.9%) were most frequently reported. The majority of events in the Investigations SOC reflected liver test abnormalities (PTs of alanine aminotransferase increased, aspartate aminotransferase increased, and blood bilirubin increased), and were similar between treatment arms. In the SOC of Infections and Infestations, COVID-19 (MSB11456: 6.0%; EU-RoActemra: 5.6%) and upper respiratory tract infections (MSB11456: 2.0%; EU-RoActemra: 3.3%) were the most common events, and were balanced by treatment arms.

In the Nervous System Disorders SOC (MSB11456: 7.9%; EU-RoActemra: 6.3%), a higher proportion of subjects in the MSB11456 treatment had events by PT of headache (MSB11456: 5.0%; EU-RoActemra: 2.0%); differences in proportions were due to a difference in a small number of subjects between treatment arms.

The proportions of subjects reporting TEAEs in other SOCs were generally similar between arms and did not cluster by PT.

Table 22. TEAEs (≥ 2% Incidence), Core Period, Safety Population

System Organ Class Preferred Term	**MSB11456 N=302 n (%)**	**EU-RoActemra N=302 n (%)**
Number of subjects with ≥ 1 TEAEs	**199 (65.9)**	**190 (62.9)**
Investigations	**65 (21.5)**	**78 (25.8)**
Alanine Aminotransferase Increased	28 (9.3)	35 (11.6)
Aspartate Aminotransferase Increased	14 (4.6)	16 (5.3)
Blood Bilirubin Increased	9 (3.0)	10 (3.3)
Blood Pressure Increased	5 (1.7)	9 (3.0)
Mycobacterium Tuberculosis Complex Test Positive	6 (2.0)	7 (2.3)
Infection and Infestations	**56 (18.5)**	**54 (17.9)**
COVID-19	18 (6.0)	17 (5.6)
Upper respiratory tract infection	6 (2.0)	10 (3.3)
Blood and Lymphatic System Disorders	**42 (13.9)**	**38 (12.6)**
Neutropenia	18 (6.0)	15 (5.0)
Leukopenia	17 (5.6)	14 (4.6)
Thrombocytopenia	7 (2.3)	8 (2.6)
Metabolism and Nutrition Disorders	**25 (8.3)**	**20 (6.6)**
Hypercholesterolemia	10 (3.3)	7 (2.3)
Hyperlipidemia	7 (2.3)	7 (2.3)
Nervous System Disorders	**24 (7.9)**	**19 (6.3)**
Headache	15 (5.0)	6 (2.0)
Gastrointestinal Disorders	**15 (5.0)**	**19 (6.3)**
Nausea	7 (2.3)	5 (1.7)
Vascular Disorders	**14 (4.6)**	**11 (3.6)**
Hypertension	10 (3.3)	7 (2.3)

Source: Adapted from Table 67, Week 55 Clinical Study Report for Study FKS456-001

Most TEAEs in the Core Period were mild or moderate in intensity (i.e. Grade 1 or 2). Similar proportions of subjects had ≥ Grade 3 TEAEs (MSB11456: 9.3%, EU-RoActemra 10.9%). Grade 3 TEAEs were balanced between treatment arms by SOC and PT, and included neutropenia (MSB11456: 2.0%; EU-RoActemra: 2.6%) and COVID-19 (MSB11456: 1.3%; EU-RoActemra: 1.7%). Other severe TEAEs occurred in 2 or fewer subjects by PT. Grade 4 events were neutropenia, hypercholesterolemia, and complete atrioventricular block/cardiogenic shock/myocardial infarction in 1 subject each in the MSB11456 arm, and neutropenia and coronary artery thrombosis in 1 subject each in the EU-RoActemra arm. All Grade 4 TEAEs were also recorded as SAEs, except for the laboratory events of neutropenia and hypercholesterolemia in the MSB11456 arm, which had no accompanying signs or symptoms. Grade 5 TEAEs included COVID-19 and acute myocardial infarction in 1 subject each and are discussed under “Deaths” above.

In the Extended Period between Weeks 24 and 30, no increase in TEAEs was observed in subjects who underwent a single transition from EU-RoActemra to MSB11456, compared to those who continued treatment with EU-RoActemra or MSB11456 (MSB11456: 20.7%; EU-RoActemra: 19.1%; EU-RoActemra/MSB11456: 15.8%). No increase in immune-related safety events was observed in the EU-RoActemra/MSB11456 arm compared to the EU-RoActemra arm, as described in Section 5.4.3.

Between Weeks 24 and 55, TEAEs were reported by 45.1% of subjects in the MSB11456 arm, 40.4% in the EU-RoActemra arm, and 41.0% in the EU-RoActemra/MSB11456 arm. Compared to subjects in the EU-RoActemra/MSB11456 arm, greater proportions of subjects in the MSB11456 and EU-Actemra treatment arms had events of COVID-19 (MSB11456: 6.8%; EU-RoActemra: 5.6%; EU-RoActemra/MSB11456: 3.6%) and upper respiratory tract infection (MSB11456: 4.1%; EU-RoActemra: 2.9%; EU-RoActemra/MSB11456: 2.2%) (Table 32). However, the differences in proportions were due to small numbers of subjects. Other TEAEs were generally balanced by treatment arm.

Similar to the Core Period, most TEAEs in the Extended Period between Weeks 24 and 55 were also mild or moderate in intensity. Grade 3 events were reported by similar proportions of subjects by treatment arm (MSB11456: 6.0%, EU-RoActemra: 5.0%, EU-RoActemra/MSB11456: 6.6%). COVID-19 (MSB11456: 2.6%; EU-RoActemra: 1.5%; EU-RoActemra/MSB11456: 1.4%) neutropenia (MSB11456: 0.8%; EU-RoActemra: 0.7%; EU-RoActemra/MSB11456: 0.7%), and leukopenia (MSB11456: 0.4%; EU-RoActemra: 1.5%; EU-RoActemra/MSB11456: 0) were the most frequently reported Grade 3 events. A single subject in the EU-RoActemra/MSB11456 treatment arm had a Grade 4 event of pelvic inflammatory disease/mechanical ileus, also considered SAEs. Grade 5 events were COVID-19 in 1 subject in the EU-RoActemra arm and acute myocardial infarction in 1 subject in the EU-RoActemra/MSB11456 arm at Study Day 363, as discussed under “Deaths”.

Healthy Subjects: In Study MS200740-0001, the types and frequencies of TEAEs reported were generally similar by SOC and PT between treatment arms and consistent with the known safety profile of US-Actemra. Grade 3 TEAEs, also recorded as SAEs, were reported in 4 subjects (appendicitis and spontaneous pneumothorax in single subjects in the MSB11456 arm; appendicitis in 1 subject in the EU-RoActemra arm; abdominal pain in 1 subject in the US-Actemra arm). There were no ≥ Grade 4 events.

In Study FKS456-002, the types and frequency of TEAEs reported were similar to the types of events reported in Study MS200740-0001 and generally balanced by SOC and PT between treatment arms. Neutropenia, the most commonly reported TEAE, was reported in a greater proportion of subjects in the MSB14456 arm than the US-Actemra arm (MSB11456: 32.3%; US-Actemra: 21.2%). High grade TEAEs of neutropenia were also observed in more subjects in the MSB11456 arm (Grade 3: 24.2%; Grade 4: 8.1%) compared to subjects in the US-Actemra arm (Grade 3: 18.2%; Grade 4: 3.0%). However, the differences in proportions were due to differences in small numbers of subjects between treatment arms. Other Grade 3 TEAEs included leukopenia (MSB11456: 1.6%; US-Actemra: 4.5%) and an event of limb injury in a single subject in the MSB11456 arm.

In Study FKS456-003, the TEAE profile was similar between the 2 presentations and consistent with the safety of MSB11456 in healthy subjects in the other 2 PK studies. Grade 3 events of alanine aminotransferase increased, tonsilitis, neutropenia, and hypersensitivity as well as a Grade 4 event of blood CPK increased were reported in single subjects after receiving the AI presentation. Grade 3 events of neutropenia were reported in 3 subjects after receiving the PFS presentation. The Grade 3 event of hypersensitivity and Grade 4 event of CPK increased were recorded as SAEs.

Dropouts and/or Discontinuations

Subjects with RA: In Study FKS456-001, 79 subjects reported 98 TEAEs that led to IMP discontinuation,185 subjects reported TEAEs that led to IMP interruption, and 55 subjects reported 65 TEAEs that led to study withdrawal.

TEAEs Leading to IMP Discontinuation

In the Core Period, a greater proportion of subjects in the MSB11456 treatment arm reported TEAEs that led to IMP discontinuation (MSB11456: 10.6%; EU-RoActemra: 7.9%), as presented in Table 23. AEs within the Investigations SOC were the most frequently reported AEs leading to IMP discontinuation, and more frequently reported by subjects in the MSB11456 arm (6.3%) compared to the EU-RoActemra arm (4.0%). The different proportions reflected small numerical differences in asymptomatic liver lab test abnormalities (discussed in detail below) and do not preclude a conclusion of similar safety between MSB11456 and EU-RoActemra. AEs leading to IMP Discontinuation were generally similar across other SOCs.

Specifically, within the Investigations SOC, there were small increases in proportions of subjects in the MSB11456 arm with AEs by PT including Alanine Aminotransferase Increased, Blood Bilirubin Increased, Blood Bilirubin Unconjugated Increased, Aspartate Aminotransferase Increased, and Gamma-Glutamyl Transferase Increased. The clinical reviewer conducted an analysis of liver-related TEAEs, by events in the Hepatobiliary Disorders SOC and the following PTs in the Investigations SOC: i.e. alanine aminotransferase increased, aspartate aminotransferase increased, bilirubin conjugated increased, blood alkaline phosphatase increased, blood bilirubin increased, blood bilirubin unconjugated increased, gamma-glutamyl transferase increased, hepatic enzyme increased, liver function test increased, transaminases increased. Based on reviewer analysis, differences in AEs leading to IMP discontinuation were due to a small increase in the proportion of subjects in the MSB11456 treatment arm discontinuing IMP for liver-related TEAEs (MSB11456: 4.0%; EU-RoActemra: 2.3%) (Table 24). Almost all of these events were in the Investigations SOC, and there were no notable differences in events in the Hepatobiliary Disorders SOC. Further, the increased proportion of subjects in the MSB11456 arm who had liver-related TEAEs that led to IMP discontinuation was not associated with increases in liver-related TEAEs overall (MSB11456: 16.2%; EU-RoActemra: 17.5%) or liver-related TE-SAEs (MSB11456: 0; EU-RoActemra: 0.3%). There were no cases that met Hy's Law criteria.

Table 23. TEAEs Leading to IMP Discontinuation, Core Period, Safety Population

System Organ Class Preferred Term	**MSB11456** **N=302** **n (%)**	**EU-RoActemra** **N=302** **n (%)**
Number of Subjects with TEAEs Leading to Discontinuation of IMP	**32 (10.6)**	**24 (7.9)**
Investigations	**19 (6.3)**	**12 (4.0)**
Mycobacterium Tuberculosis Complex Test Positive	6 (2.0)	6 (2.0)
Alanine Aminotransferase Increased	4 (1.3)	2 (0.7)
Blood Bilirubin Increased	4 (1.3)	2 (0.7)
Blood Bilirubin Unconjugated Increased	3 (1.0)	2 (0.7)
Aspartate Aminotransferase Increased	3 (1.0)	1 (0.3)
Gamma-Glutamyl Transferase Increased	2 (0.7)	1 (0.3)
False Positive Tuberculosis Test	1 (0.3)	0
Mycobacterium Tuberculosis Complex Test	1 (0.3)	0
Infections and Infestations	**3 (1.0)**	**3 (1.0)**
Latent tuberculosis	2 (0.7)	2 (0.7)
COVID-19	0	1 (0.3)
Furuncle	1 (0.3)	0
Cardiac Disorders	**1 (0.3)**	**3 (1.0)**
Acute Myocardial Infarction	0	1 (0.3)
Atrioventricular Block Complete	1 (0.3)	0
Cardiogenic Shock	1 (0.3)	0
Coronary Artery Stenosis	0	1 (0.3)
Coronary Artery Thrombosis	0	1 (0.3)
Myocardial Infarction	1 (0.3)	0

Skin and Subcutaneous Tissue Disorders	**3 (1.0)**	**1 (0.3)**
Erythema	1 (0.3)	0
Pruritus	1 (0.3)	0
Rash Erythematous	0	1 (0.3)
Skin Ulcer	1 (0.3)	0
General Disorders and Administration Site Conditions	**1 (0.3)**	**2 (0.7)**
Injection Site Erythema	1 (0.3)	1 (0.3)
Injection Site Pruritus	0	1 (0.3)
Injection Site Swelling	0	1 (0.3)
Cardiac Disorders	**1 (0.3)**	**1 (0.3)**
Atrioventricular block complete	1 (0.3)	0
Cardiogenic shock	1 (0.3)	0
Coronary artery thrombosis	0	1 (0.3)
Myocardial infarction	1 (0.3)	0
Hepatobiliary Disorders	**1 (0.3)**	**1 (0.3)**
Autoimmune hepatitis	0	1 (0.3)
Hepatic steatosis	0	1 (0.3)
Hyperbilirubinemia	1 (0.3)	0
Musculoskeletal and Connective Tissue Disorders	**1 (0.3)**	**1 (0.3)**
Rheumatoid Arthritis	0	1 (0.3)
Spinal Stenosis	1 (0.3)	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**1 (0.3)**	**1 (0.3)**
Basal cell carcinoma	0	1 (0.3)
Follicular thyroid cancer	1 (0.3)	0
Blood and Lymphatic System Disorders	**1 (0.3)**	**0**
Leukopenia	1 (0.3)	0
Immune System Disorders	**1 (0.3)**	**0**
Drug Hypersensitivity	1 (0.3)	0
Reproductive System and Breast Disorders	**0**	**1 (0.3)**
Ovarian Cyst	0	1 (0.3)
Respiratory, Thoracic, and Mediastinal Disorders	**0**	**1 (0.3)**
Lung Infiltration	0	1 (0.3)

Source: Adapted from Table 78, Week 55 Clinical Study Report for Study FKS456-001

Table 24. Liver-Related TEAEs Leading to IMP Discontinuation, Core Period, Safety Population

System Organ Class Preferred Term	MSB11456 N=302 n (%)	EU-RoActemra N=302 n (%)
Number of Subjects with Liver-Related TEAEs Leading to Discontinuation of IMP	**12 (4.0)**	**7 (2.3)**
Investigations	**11 (3.6)**	**6 (2.0)**
Alanine Aminotransferase Increased	4 (1.3)	2 (0.7)
Blood Bilirubin Increased	4 (1.3)	2 (0.7)
Blood Bilirubin Unconjugated Increased	3 (1.0)	2 (0.7)
Aspartate Aminotransferase Increased	3 (1.0)	1 (0.3)
Gamma-Glutamyl Transferase Increased	2 (0.7)	1 (0.3)
Hepatobiliary Disorders	**1 (0.3)**	**1 (0.3)**
Autoimmune hepatitis	0	1 (0.3)
Hepatic steatosis	0	1 (0.3)
Hyperbilirubinemia	1 (0.3)	0

Source: Clinical Reviewer, JMP analysis of Week 55 ADAE dataset for Study FKS456-001

The most common reason for IMP discontinuation, both in the Core Period and Study FKS456-001 overall, was conversion to a positive TB test on scheduled testing at Week 24. As noted in Section 6.2.1 ("Subject Disposition"), 20 subjects discontinued IMP for conversion to a positive TB test as specified in the protocol discontinuation criteria. Among the 20, 18 subjects (balanced by treatment arm) were tested at Week 24 as per protocol and were categorized as having had a TEAE (i.e. PTs of Mycobacterium tuberculosis complex test positive, latent tuberculosis, or Mycobacterium tuberculosis complex test) in the Core Period. The other 2 subjects (1 each in the MSB11456 and EU-RoActemra arms) had TB testing performed after starting Extended Period treatment and were categorized as having had TEAEs in the Extended Period that led to IMP discontinuation; these were also considered protocol violations.

Between Weeks 24 and 30 in the Extended Period, TEAEs that led to IMP discontinuation were similar by treatment arm, without an increase in the group that underwent a single transition from EU-RoActemra to MSB11456 compared to those who continued treatment with EU-RoActemra or MSB11456 (MSB11456: 1.9%; EU-RoActemra: 0.7%; EU-RoActemra/MSB11456: 1.4%). In the EU-RoActemra arm, 1 subject discontinued IMP for the TEAE of Mycobacterium tuberculosis complex test positive discussed above. Two (2) subjects in the EU-RoActemra/MSB11456 arm discontinued IMP for events of blood bilirubin unconjugated increased. In the MSB11456 arm, 1 subject discontinued IMP for an injection site reaction (erythema, pain, pruritus, and swelling), 2 subjects discontinued for alanine aminotransferase increased, 1 subject discontinued for Mycobacterium tuberculosis complex test positive (as discussed above), and 1 subject discontinued for blood bilirubin unconjugated increased.

Between Weeks 24 and 55, a greater proportion of subjects in the EU-RoActemra/MSB11456 arm reported TEAEs that led to IMP discontinuation compared to subjects in either the MSB11456 or EU-RoActemra treatment arms (MSB11456: 3.4%; EU-RoActemra: 2.9%; EU-RoActemra/MSB11456: 7.2%) (Table 33). However, the differences between treatment arms were due to small numbers of subjects and no clustering was observed by SOC or PT. Events by PT in more than 1 subject that led to IMP discontinuation included blood bilirubin unconjugated increased, blood bilirubin increased, and alanine aminotransferase increased, and were similar across the treatment arms.

TEAEs Leading to Study Withdrawal

In the Core Period, a slightly greater proportion of subjects in the MSB11456 treatment arm reported TEAEs that led to study withdrawal (MSB11456: 7.3%; EU-RoActemra: 5.6%). Based on the clinical reviewer's analysis, the difference was due to a slightly greater proportion of subjects with liver-related TEAEs in the MSB11456 treatment arm (MSB11456: 2.6%; EU-RoActemra: 1.3%), paralleling the trend for TEAEs that led to IMP discontinuation, and largely due to events in the Investigations SOC. There was one subject with TEAE leading to study withdrawal within the hepatobiliary disorders SOC in each treatment arm. As discussed above, while there were small differences in liver-related investigations leading to IMP discontinuation and study withdrawal, differences in number of subjects between arms were small and these were not associated with hepatobiliary events, nor an imbalance in liver-related TEAEs or SAEs.

In the Extended Period between Week 24 and 55, the proportion of subjects in the EU-RoActemra/MSB11456 and EU-RoActemra arms with TEAEs that led to study withdrawal were similar, and higher than in the MSB11456 arm (MSB11456: 1.9%; EU-RoActemra: 3.7%; EU-RoActemra/MSB11456: 4.3%). The types and frequencies of TEAEs that led to study withdrawal were generally balanced by treatment arm.

TEAEs that led to study withdrawal for more than 1 subject in either treatment period included PTs related to a positive TB test (i.e. Mycobacterium tuberculosis complex test positive, latent tuberculosis, or Mycobacterium tuberculosis complex test) and liver lab test abnormalities (i.e. alanine aminotransferase increased and blood bilirubin increased). Risks of infections, including TB, and elevated liver enzymes are labeled risks of US-Actemra treatment.

TEAEs Leading to IMP Interruption

In the Core Period, 124 subjects had IMP interrupted, balanced by treatment arm (MSB11456: 20.5%, EU-RoActemra: 20.5%). The most frequently reported TEAEs that led to IMP interruption were COVID-19, upper respiratory tract infection, alanine

aminotransferase increased, neutropenia, and leukopenia, all generally balanced by treatment arm. Other events by PT were reported in 2 or fewer subjects.

In the Extended Period between Weeks 24 and 55, 61 subjects had IMP interrupted (MSB11456: 13.2%; E.U.-Ro-Actemra: 9.6%; EU-RoActemra/MSB11456: 9.4%). The most common TEAEs that led to IMP interruption were generally balanced by treatment arm, similar by PT to those in the Core Period, and included COVID-19, upper respiratory tract infection, leukopenia, and thrombocytopenia. All other reported events occurred in 2 or fewer subjects. There was no increase in TEAEs that led to IMP interruption following the single transition in the EU-RoActemra/MSB11456 arm, as compared to the arms that continued on EU-RoActemra and MSB11456.

Healthy Subjects: Across the 3 comparative PK studies, the numbers of healthy subjects who discontinued IMP due to TEAEs was small and did not cluster by PT or SOC. No discontinuations due to AEs were reported in either Study MS200740-0001 or Study FKS456-002. In Study FKS456-003, 7 healthy subjects discontinued IMP due to TEAEs. Four (4) subjects discontinued for events of Mycobacterium TB complex test positive: 1 subject after receiving MSB11456 by PFS and 3 subjects after receiving MSB11456 by AI. One (1) subject each discontinued for events of pharyngitis and SARS-CoV-2 test positive (also recorded as a SAE as described above) after receiving MSB11456 by PFS, and 1 subject discontinued for blood creatinine phosphokinase increased after receiving MSB11456 by AI.

Adverse Events of Special Interest (AESIs)

As discussed in Section 6.3.1, protocol-defined AESIs included serious infections requiring administration of intravenous antibiotics, hypersensitivity (i.e. an AE within 24 hours of an injection, excluding injection site reactions and considered related to treatment) and anaphylaxis (according to Sampson's criteria), and AEs leading to the interruption of study treatment, permanent discontinuation of study treatment, or withdrawal from the study.

Subjects with RA: In the Core Period, 88 (29.1%) and 81 (26.8%) subjects in the MSB11456 and EU-RoActemra treatment arms, respectively, reported at least 1 AESI, as shown in Table 25. The majority of AESIs were TEAEs that led to IMP interruption (62 subjects [20.5%] each in the MSB11456 and EU-RoActemra treatment arms), and are discussed in the "Dropouts and/or Discontinuations" subsection above. AESI of serious infections requiring IV antibiotics were reported in similar proportions of subjects in each arm (MSB11456: 12.9%; EU-RoActemra: 10.6%). The most common AESI of serious infection was COVID-19, balanced by treatment arm (MSB11456: 6.0%; EU-RoActemra: 5.6%).

Table 25. AESIs (≥ 1% Incidence), Core Period, Safety Population

System Organ Class Preferred Term	MSB11456 N=302 n (%)	EU-RoActemra N=302 n (%)
Number of Subjects with ≥ 1 AESI	**88 (29.1)**	**81 (26.8)**
Infections and Infestations	**39 (12.9)**	**32 (10.6)**
COVID-19	18 (6.0)	17 (5.6)
Upper Respiratory Tract Infection	5 (1.7)	6 (2.0)
Investigations	**25 (8.3)**	**28 (9.3)**
Alanine Aminotransferase Increased	6 (2.0)	10 (3.3)
Mycobacterium Tuberculosis Complex Test Positive	6 (2.0)	6 (2.0)
Blood Bilirubin Increased	6 (2.0)	3 (1.0)
Aspartate Aminotransferase Increased	4 (1.3)	3 (1.0)
Blood and Lymphatic System Disorders	**11 (3.6)**	**11 (3.6)**
Neutropenia	8 (2.6)	7 (2.3)
Lung Infiltration	5 (1.7)	3 (1.0)

Source: Adapted from Table 85, Week 55 Clinical Study Report for Study FKS456-001

No AESIs of anaphylaxis were reported and a single Grade 2 drug hypersensitivity was reported in 1 MSB11456-treated subject. Hypersensitivity and anaphylaxis were also assessed by SMQ analysis. There were no TEAEs within the SMQ of anaphylactic reaction during the Core or Extended Periods. During the Core Period, TEAEs within the hypersensitivity SMQ were reported in similar proportions of subjects in each treatment arm (MSB11456: 3.6%; EU-RoActemra: 5.5%). Reported PTs within the SMQ analysis included skin and subcutaneous tissue disorders (pruritus, dermatitis, rash, dermatitis contact, rash pruritic, dermatitis allergic, erythema and rash erythematous), immune system disorders (contrast media allergy, drug hypersensitivity), respiratory, thoracic and mediastinal disorders (rhinitis allergic), gastrointestinal disorders (mouth ulceration), general disorders and administration site conditions (swelling face) and vascular disorders (flushing). None of TEAEs by PT associated with an AESI of hypersensitivity by the SMQ analysis were higher than Grade 2 in severity. As discussed in Section 5.4.3, all subjects with hypersensitivity were ADA positive, except for 1 in the MSB11456 arm with a TEAE by PT of drug hypersensitivity.

In the Extended Period between Weeks 24 and 30, there was no increase in AESIs in subjects in the EU-RoActemra/MSB11456 arm compared to the MSB11456 or EU-RoActemra arms (MSB11456: 7.1%; EU-RoActemra: 5.9%; EU-RoActemra/MSB11456: 6.5%). Proportions of subjects with AESI of serious infections were similar by treatment arm. Similar to the Core Period, small proportions of subjects had AESIs of hypersensitivity by SMQ analysis, generally balanced across treatment arms (MSB11456: 1.5%; EU-RoActemra: 1.5%; EU-RoActemra/MSB11456: 2.2%), and all were ADA positive subjects. The types of TEAEs by PT associated with AESIs of hypersensitivity by SMQ analysis were also generally similar across treatment groups and to those in the Core Period.

Between Weeks 24 and 55, similar proportions of subjects reported at least 1 AESI across treatment arms (MSB11456: 15.8%; EU-RoActemra: 12.5%; EU-RoActemra/MSB11456: 15.1%) as shown in Table 34. Serious infections were more frequently reported in the MSB11456 arm; COVID-19 was the most frequently reported AESI of serious infection. A numerically greater proportion of subjects in the EU-RoActemra/MSB11456 arm (6.7%) had AESIs of hypersensitivity by SMQ analysis compared to the EU-RoActemra (3.1%) and MSB11456 (2.1%) arms. SMQ hypersensitivity TEAEs more frequently reported in the EU-RoActemra/MSB11456 arm include Gastrointestinal Disorders (1 subject each with cheilitis, stomatitis) and General Disorders and Administration Site Conditions (1 subject each with injection site hypersensitivity and swelling face). All SMQ hypersensitivity TEAEs in all treatment arms were in ADA positive subjects. Similar to the Core Period, none of the TEAEs by PT associated with a AESI of hypersensitivity by SMQ analysis in the Extended Period were higher than Grade 2 in severity.

While not pre-specified as AESIs for Study FKS456-001, gastrointestinal perforation and hepatotoxicity are also known risks for US-Actemra. There were no events of drug-induced liver injury (DILI) or liver abnormalities meeting Hy's Law criteria. One (1) AE of gastric perforation was reported in a single subject prior to randomization as discussed under "Deaths".

Healthy Subjects: In Study MS200740-0001, the majority of AESIs were injection site reactions considered related to study treatment by the Investigator (MSB11456: 7.8%, US-Actemra: 1.3%, EU-RoActemra: 5.3%). All injection site reactions considered AESIs were Grade 1 in severity with injection site erythema being the most common PT (MSB11456: 6.5%; US-Actemra: 1.3%; EU-RoActemra: 5.3%). For AESIs of serious infection, single subjects in the MSB11456 and EU-RoActemra arms had Grade 3 events of appendicitis perforated. No AESIs of hypersensitivity reaction were reported.

In Study FKS456-002, no healthy subjects reported AESIs.

In Study FKS456-003, 2 subjects experienced singular AESIs: 1 subject with a SAE of hypersensitivity after receiving IMP via AI and 1 subject with COVID-19 after receiving IMP via PFS. Both AESIs are described under SAEs above.

No events of gastrointestinal perforation or DILI/Hy's Law were reported in the PK studies.

Overall, in the MSB11456 development program, AESI were balanced by treatment arm. Serious infections requiring IV antibiotics were similar. There were no AESIs of anaphylaxis, and the incidence of hypersensitivity, based on hypersensitivity TEAEs and SMQ hypersensitivity analysis, was low and comparable between MSB11456, EU-RoActemra, and/or US-Actemra. Risks of serious infections, hypersensitivity, and anaphylaxis are consistent with the known safety profile of tocilizumab and included in the labeled warnings and precautions of US-Actemra.

6.3.3. Additional Safety Evaluations

Laboratory Findings

Subjects with RA: In Study FKS456-001, clinical chemistry (including lipids and C-reactive protein [CRP]), hematology (including coagulation parameters and erythrocyte sedimentation rate [ESR]), and urinalysis assessments were performed at Baseline, Weeks 2, 4, 8, 12, 16, and 24 in the Core Period and at Weeks 30, 42, 52 in the Extended Period. Week 24 assessments were used as baseline assessments for the Extended Period.

Clinical Chemistry

Small changes in mean and median values for clinical chemistry parameters (albumin, alkaline phosphatase; AST and ALT; total, direct and indirect bilirubin; calcium; total, HDL and LDL cholesterol and triglycerides; creatine kinase; creatinine; GGT; LDH; potassium; phosphate; total protein; sodium; urea nitrogen) were observed in both the Core and Extended Periods. The observed changes were generally similar between treatment arms in both treatment periods. No cases of DILI based on Hy's law criteria were reported in Study FKS456-001 or elsewhere in the MSB11456 clinical development program.

Clinical chemistry values that worsened during the Core Period from Grade < 3 to Grade ≥ 3 occurred in small numbers and in similar proportions of subjects in both the MSB11456 and EU-RoActemra arms and included hypertriglyceridemia (0.7% and 2.0%, respectively), hyperkalemia (0 and 1.3%), increased cholesterol (0.3% and 0.7%), increased creatinine (0 and 1.0%), increased GGT (0.7% and 0), increased creatine kinase (0 and 0.7%), and hypocalcemia (0 and 0.3%).

In the Extended Period, clinical chemistry values that worsened from extended baseline from Grade < 3 to Grade ≥ 3 also occurred in small numbers in similar proportions of subjects in the MSB11456, EU-RoActemra and EU-RoActemra/MSB11456 arms and were of similar types and frequencies to the Core Period.

Mean changes in CRP were generally similar between MSB11456 and EU-RoActemra treatment arms at the end of the Core Period (-13.04 mg/L and -10.36 mg/L, respectively), and between MSB11456, EU-RoActemra, and the EU-RoActemra/MSB11456 arm between Weeks 24 and 52 (0.78 mg/L, 0.03 mg/L, and 1.82 mg/L, respectively).

Hematology

No notable differences were observed in mean and median values for hematology parameters (aPTT, PT/INR, hemoglobin, hematocrit, erythrocytes, platelets, leukocytes, lymphocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, mean corpuscular volume) between treatment arms in either the Core or Extended Period.

In the Core Period, hematology values that worsened from Grade < 3 to Grade ≥ 3 occurred in small numbers and in similar proportions of subjects in the MSB11456 and EU-RoActemra treatment arms. These included decreased neutrophils (2.3% and 2.6%, respectively), increased PT/INR (0.7% and 1.0%), anemia (0.7% and 0.3%), decreased lymphocytes (0 and 0.7%), and decreased leukocytes (0.3% in both treatment arms). In the Extended Period, hematology values that worsened from Grade < 3 to Grade ≥ 3 also occurred in similar proportions of subjects in the MSB11456, EU-RoActemra, and EU-RoActemra/MSB11456 arms respectively and were of similar types and frequencies to those observed in the Core Period.

Mean changes in ESR were generally similar between MSB11456 and E.U-RoActemra treatment arms at the end of the Core Period (-29.83 mm/h and -29.25 mm/h, respectively), and generally similar between MSB11456, EU-RoActemra, and the EU-RoActemra/MSB11456 arm between Weeks 24 and 52 (-0.82 mm/h, -0.56 mm/h, and 0.12 mm/h, respectively).

Urinalysis

No notable differences were observed between treatment arms in either the Core or Extended Periods.

Healthy Subjects: No notable differences in clinical chemistry, hematology, or urinalysis laboratory assessments were observed between treatment arms in the 3 PK studies (Studies MS200740-0001, FKS456-002, and FKS456-003).

Overall, the types and frequencies of observed laboratory changes were similar between MSB11456 and EU-RoActemra in subjects with RA, and similar between MSB11456, US-Actemra and/or EU-RoActemra in heathy subjects.

Vital Signs

Subjects with RA: In Study FKS456-001, mean and median values and changes from baseline for systolic blood pressure, diastolic blood pressure, heart rate, respiration rate and body temperature were similar between treatment arms in both the Core and Extended Periods. No notable differences were observed either in the proportions of subjects with maximal on-treatment changes in systolic and diastolic blood pressure, heart rate, respiration rate, or temperature in either treatment period.

Healthy Subjects: In the PK studies (Studies MS200740-0001, FKS456-002, and FKS456-003), no clinically significant changes over time or differences between treatment arms were observed for systolic blood pressure, diastolic blood pressure, heart rate, or body temperature.

Electrocardiograms (ECGs)

Subjects with RA: In Study FKS456-001, ECGs were collected at Screening and Weeks 24 and 52. A single subject in the EU-RoActemra arm had a clinically significant abnormality documented at Week 52. No clinically significant ECG abnormalities were reported in any subjects exposed to MSB11456 in either treatment period.

Healthy Subjects: No clinically significant abnormalities were observed in healthy subjects in the 3 PK studies (Studies MS200740-0001, FKS456-002, and FKS456-003).

6.4. Clinical Conclusions on Immunogenicity

The immunogenicity evaluation included qualitative and quantitative measurement of ADAs and NAbs in healthy subjects (from single dose PK studies with IV and SC forms of IMP) and in subjects with RA (repeat doses of SC IMP for up to 52 weeks), and an assessment in subjects with RA of the impact of ADA on PK, efficacy and safety. In Study FKS456-001, ADA and NAb incidence were similar between MSB11456 and EU-RoActemra treatment arms up to Week 24. After the single transition, ADA incidence was similar amongst the groups, although NAb were numerically higher in the EU-RoActemra/MSB11456 arm compared to the arms that continued without transition. ADA incidence had a similar effect on PK across the treatment arms, during the Core Period and following the single transition in the EU-RoActemra/MSB11456 arm compared to those who continued on EU-RoActemra. The assessment of the impact of ADA on efficacy and safety is limited by the small numbers of ADA negative subjects in the study. However, ADA and NAb did not impact efficacy based on DAS28-ESR change from baseline, and the proportions of subjects with potential immune-related safety events, including events of ISR and hypersensitivity, were generally small and did not increase following the single transition.

Collectively, data from the comparative clinical study and the comparative PK studies support the conclusion that MSB11456 was similar to US-Actemra and/or EU-RoActemra in the production of ADA and the impact of ADA on PK, efficacy and safety. Refer to Section 5.4 for a detailed discussion of the results of the immunogenicity assessments.

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6.5. Extrapolation of Data to Support Biosimilarity in Other Conditions of Use

The Applicant submitted data and information in support of a demonstration that MSB11456 is highly similar to US-Actemra notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between MSB11456 and US-Actemra in terms of safety, purity and potency.

The Applicant is seeking licensure of MSB11456 for the following indication(s) for which US-Actemra has been previously licensed and for which MSB11456 has not been directly studied:

1. Adults with giant cell arteritis
2. Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis
3. Patients 2 years of age and older with active systemic juvenile idiopathic arthritis

Due to unexpired orphan exclusivity, the Applicant is not currently seeking licensure for MSB11456 for following indications for which US-Actemra has also been approved:

1. Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR)-T cell-induced severe or life-threatening cytokine release syndrome (CRS)
2. Slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD)

In addition, the Applicant is not seeking licensure for MSB11456 for hospitalized patients with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation.

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of MSB11456 as a biosimilar for each indication for which licensure is sought and for which US-Actemra has been previously approved. This Applicant's justification was evaluated and considered adequate, as summarized below.

Therefore, the totality of the evidence provided by the Applicant supports licensure of MSB11456 for each of the following indications for which Fresenius Kabi USA, LLC. is seeking licensure of MSB11456: giant cell arteritis, patients 2 years of age and older

with active polyarticular juvenile idiopathic arthritis, and patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

Mechanism of Action

The Applicant provided data to support that MSB11456 has the same known and potential mechanisms of action as US-Actemra, which supports extrapolation to indications not directly studied in the MSB11456 clinical program. Tocilizumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and has been shown to competitively inhibit IL-6-mediated signaling through these receptors. This MOA is common in all approved indications of US-Actemra. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. Elevated serum IL-6 levels are present in RA, PJIA, SJIA, and GCA. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis, PJIA, and SJIA. IL-6 is also associated with manifestations of SJIA (e.g., fever, rash, lymphadenopathy, hepatosplenomegaly, anemia, and poor growth). The biological activities of MSB11456 and US-Actemra were evaluated by a comprehensive set of comparative functional and binding assays. The data provided by the Applicant showed that Fab and Fc binding and bioactivity properties and the inhibition of IL-6-dependent signaling through Janus-activated kinase-signal transducer and activator of transcription (JAK-STAT) pathways are similar between MSB11456 and US-Actemra. The product quality reviewers concluded that the comparative analytical assessment was acceptable.

The Applicant provided adequate information to support that MSB11456 has the same known and potential mechanisms of action as US-Actemra for RA, GCA, PJIA, and SJIA.

Pharmacokinetics (PK)

PK similarity was demonstrated in Study MS200740-00001 and Study FKS456-002, both randomized, double-blind, parallel group, single dose PK similarity studies conducted in healthy volunteers. The clinical pharmacology review team concluded that the data from Studies MS200740-0001 and FKS456-002 support a demonstration of PK similarity of SC MSB11456 to US-Actemra, and IV MSB11456 to US-Actemra, respectively (Refer to Section 5.3). There were no product-related attributes that would increase uncertainty that the PK/biodistribution may differ between MSB11456 and US-Actemra in the indications sought for licensure. Therefore, a similar PK profile would be expected between MSB11456 and US-Actemra in patients with GCA, PJIA, and SJIA.

The Applicant provided adequate justification that a similar PK profile is expected between MSB11456 and US-Actemra for GCA, PJIA, and SJIA.

Immunogenicity

In the MSB11456 development program, immunogenicity was evaluated in populations that were considered sensitive for detecting meaningful differences (RA and healthy subjects). Immunogenicity was found to be similar when comparing SC MSB11456 and US-Actemra in PK similarity Study MS200740-0001 in healthy subjects, comparing IV MSB11456 and US-Actemra in PK similarity Study FKS456-002 in healthy subjects, and between MSB11456 and EU-RoActemra in the comparative clinical study FKS456-001 in patients with RA. Therefore, similar immunogenicity would be expected between MSB11456 and US-Actemra in patients across all the indications being sought for licensure.

The Applicant provided adequate justification that similar immunogenicity is expected between MSB11456 and US-Actemra for GCA, PJIA, and SJIA.

Toxicity

The Applicant demonstrated that are no clinically meaningful differences in safety between MSB11456 and EU-RoActemra in subjects with RA and between MSB11456, US-Actemra, and EU-RoActemra following single SC doses in healthy subjects and between MSB11456 and US-Actemra following single IV doses in healthy subjects. Coupled with the demonstration of analytical and PK similarity between MSB11456, US-Actemra, and EU-RoActemra, a similar safety profile would be expected in across all indications being sought for licensure.

The Applicant provided adequate justification that a similar safety profile would be expected between MSB11456 and US-Actemra for GCA, PJIA, and SJIA.

Additional factors considered (if applicable)

None

Conclusions

DRTM concludes that the Applicant has provided sufficient scientific justification (based on the mechanism of action, pharmacokinetics, immunogenicity and toxicity profile) for extrapolation of the data and information submitted in the application to support licensure of MSB11456 for each of the following indications for which Fresenius Kabi USA, LLC. is seeking licensure of MSB11456: giant cell arteritis, patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis, and patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

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7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, tocilizumab-aazg, was found to be conditionally accepted by the Agency. See DMEPA review dated March, 3, 2023 for full details.

7.2. Proprietary Name

The proposed proprietary name for MSB11456 is conditionally approved as Tyenne. This name has been reviewed by the Division of Medication Error and Prevention Analysis 1 (DMEPA), who concluded the name was acceptable. See the DMEPA review dated November 30, 2022 for full details.

7.3. Other Labeling Recommendations

MSB11456 is proposed as a biosimilar to US-Actemra. The Applicant is seeking licensure for the following indications, for which US-Actemra has been previously approved: rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis in patients 2 years of age and older, and systemic juvenile idiopathic arthritis in patients 2 years of age and older.

The Applicant is not seeking licensure for the following indications for which US-Actemra has been previously approved: systemic sclerosis-associated interstitial lung disease (SSc-ILD) in adults and cytokine release syndrome (CRS) in adults and pediatric patients 2 years of age and older, due to existing orphan exclusivity for the reference product for these indications. The Applicant is also not seeking licensure for treatment of adults with COVID-19. The Applicant's proposed labeling does not include information related to indications for SSc-ILD, CRS, or COVID-19.

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

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

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

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

The Applicant has adequately disclosed financial interests and arrangements with the investigators and subinvestigators. Form 3454 is noted in Section 14.2 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the Applicant.

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9. Advisory Committee Meeting and Other External Consultations

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

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10. Pediatrics

The Applicant's iPSP was discussed at the PeRC meeting on December 22, 2020 and subsequently reviewed at the PeRC meeting on March 2, 2021. The PeRC agreed with the Applicant's plans to provide an assessment via extrapolation for pediatric patients 2 to less than 17 years of age with PJIA and SJIA and to request a partial waiver for

pediatric patients from birth to less than 2 years of age because necessary studies are impossible or highly impractical. PeRC agreed that because the reference product has a full waiver for GCA and there is no information in the reference product labeling for pediatric patients with GCA, as described in A.I.16 in the FDA guidance "New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)" the applicant does not need to request a waiver for GCA. The pediatric study plan was agreed upon on March 5, 2021.

The Applicant has provided the pediatric assessment for PJIA ages 2 years and older, and SJIA ages 2 years and older, based on a demonstration of biosimilarity and providing an adequate scientific justification to support the extrapolation of data and information to support licensure (refer to Section 6.5). As the approved labeling for US-Actemra includes pediatric information for SJIA under 2 years of age, PREA is addressed based on the inclusion of the relevant pediatric information in the labeling for MSB11456. The requested partial waiver for pediatric patients from birth to less than 2 years of age with PJIA is not necessary as the labeling for US-Actemra does not include adequate pediatric information and PREA requirements were waived for PJIA under 2 years for US-Actemra. Additionally, the currently proposed presentations are adequate for pediatric dosing for the age ranges proposed.

This application was discussed at the PeRC meeting on March 28, 2023. The PeRC agreed with the Division's recommendation that the pediatric assessment for GCA, RA, SJIA, and PJIA is considered complete and no pediatric studies will be required under the Pediatric Research Equity Act (PREA).

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11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None.

11.2. Recommendations for Postmarket Requirements and Commitments

Not applicable.

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Clinical Reviewer

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Clinical Team Leader/CDTL

12. Comments to Applicant

The regulatory action for this BLA is Complete Response for the following deficiency.

DEFICIENCY

Following inspections of Fresenius Kabi Austria GmbH, Graz, Austria (FEI: 3003708554) and (b) (4) listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

ADDITIONAL COMMENTS

The following comments/recommendations that are not approvability issues were provided to the Applicant:

1. Revise the method for container closure integrity testing of MSB11456 drug product in vial to include a positive control that reflects a breach defect ≤ 20 µm and update the application accordingly.

2. The acceptance criteria for oxidized variants by RP-UPLC, degree of coloration, and device performance attributes for the prefilled syringe (b) (4) and autoinjector in the drug substance and/or drug product specifications are based on a limited number of MSB11456 batches, thus re-evaluation of the acceptance criteria for these attributes is needed after data from sufficient MSB11456 drug substance and/or drug product batches are available. Submit a rationale for the number of batches needed and a statistical plan that will be used to evaluate the results for each assessment.

13. Division Director or Designated Signatory Comments

I concur with the review and conclusions by the review team. The regulatory action is Complete Response.

Author:
Rachel Glaser, M.D.
DRTM Associate Director for Therapeutic Review

14. Appendices

14.1. References

Burmester GR, Rubbert-Roth A, Cantagrel A, et al., 2014, A randomized, double-blind, parallel group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying anti-rheumatic drugs in subjects with moderate to severe rheumatoid arthritis (SUMMACTA) study, Ann Rheum Dis, 73(1):69-74.

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14.2. Financial Disclosure

The Applicant has adequately disclosed potential financial interests/arrangements with clinical investigators as recommended in the FDA Guidance for Industry *Financial Disclosure by Clinical Investigators*.[5] The provided financial certification and disclosure forms attest that no clinical investigators reported disclosable financial interests or arrangements that would result in a conflict of interest. Review of the documents does not raise concerns regarding the integrity of the submitted data to the current application and do not affect the review or recommendation for action.

[5]For further information, see Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators

Covered Clinical Study: MS200740-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 25		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: FKS456-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 280		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: FKS456-002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 20		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: FKS456-003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 22		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.3. Clinical Pharmacology Appendices

14.3.1. Pharmacodynamics Exploratory Assessment

Pharmacodynamic (PD) response was evaluated in healthy subjects in Study MS200740-0001 as exploratory analyses. The selected exploratory PD endpoints were soluble interleukin-6 receptor (sIL-6R) and C-reactive protein (CRP). For completeness of presenting the overall study findings, the results of the PD analyses are presented in Table 26 and Table 27 below. The concentration time profiles for sIL-6R and CRP are presented in Figure 17 and Figure 18 below.

For each exploratory PD biomarker, the results were comparable between treatment groups.

Table 26. Summary of Statistical Analyses for Assessment of Baseline Adjusted Soluble Interleukin-6 Receptor Similarity (Study MS200740-0001)

Parameter	Geometric Mean (%CV)			Geometric Mean Ratio* (90% CI)		
	MSB11456 (N=230)	US-Actemra (N=228)	EU-RoActemra (N=224)	MSB11456 vs US-Actemra	MSB11456 vs EU-RoActemra	EU-RoActemra vs. US-Actemra
$AUEC_{sIL-6R}$ (ng.h/mL)	94900 (43.2)	90200 (65.3)	96500 (34.8)	106.16 (99.18, 113.63)	97.85 (91.39, 104.76)	108.50 (101.31, 116.18)
E_{max} (ng/mL)	304 (31.2)	298 (42.8)	309 (24.9)	102.66 (97.72, 107.86)	98.28 (93.53, 103.27)	104.46 (99.39, 109.78)

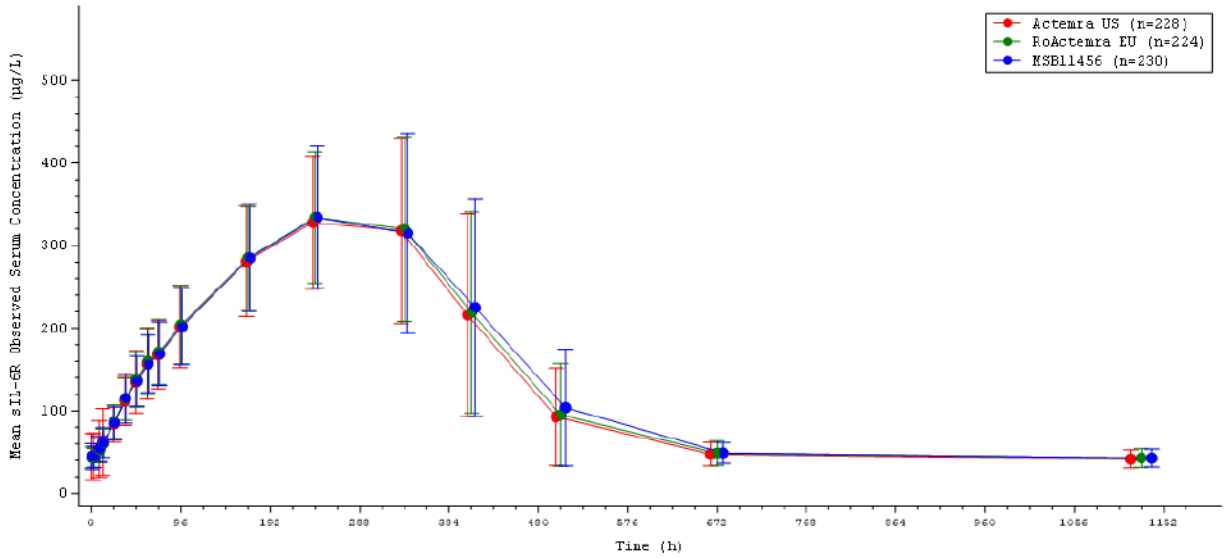
*Presented as percent
Source: Applicant analysis; Table 21 and Table 15.5.2.1 in Clinical Study Report for Study MS200740-0001

Table 27. Summary of Statistical Analyses for Assessment of Baseline Adjusted C-Reactive Protein Similarity (Study MS200740-0001)

Parameter	Arithmetic Mean (%CV)			Arithmetic Mean Difference* (90% CI)		
	MSB11456 (N=230)	US-Actemra (N=228)	EU-RoActemra (N=224)	MSB11456 vs US-Actemra	MSB11456 vs EU-RoActemra	EU-RoActemra vs. US-Actemra
$AUEC_{CRP}$ (ug.h/mL)	-160 (-2407.7)	-66.9 (-2742.8)	-466 (-1167.7)	-77.2 (-691, 537)	305 (-311, 922)	-382 (-1000, 237)
E_{max} (ug/mL)	-1.09 (-313.5)	-0.96 (-158.1)	-1.44 (-391.2)	-0.0989 (-0.699, 0.501)	0.347 (-0.255, 0.949)	-0.446 (-1.05, 0.158)

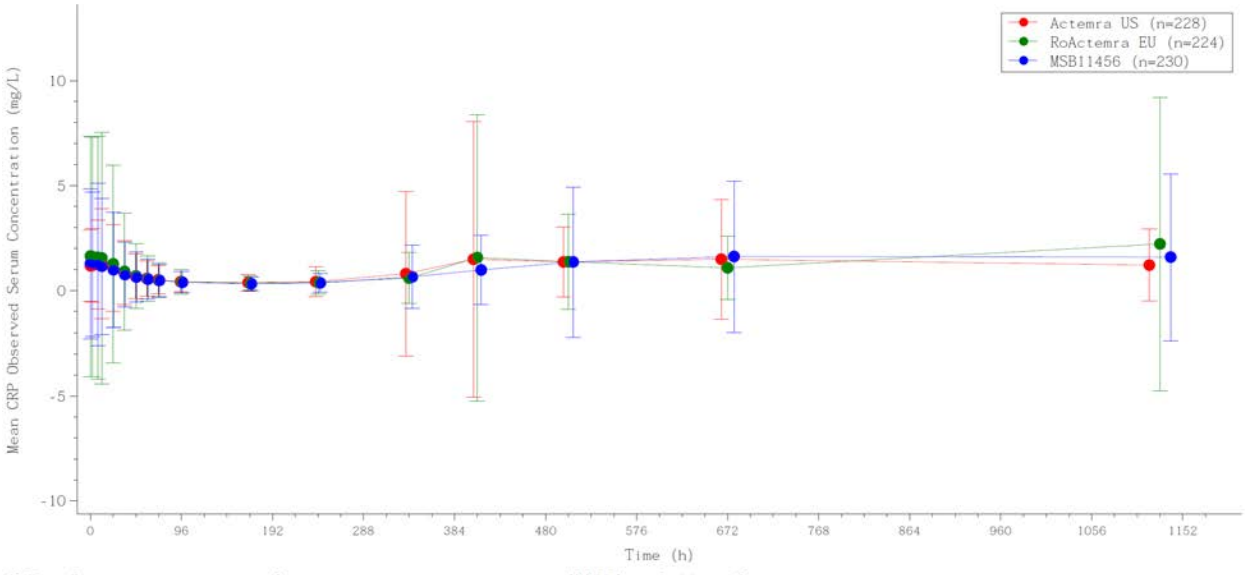
*Presented as percent
Source: Applicant analysis; Table 22 and Table 15.5.2.2 in Clinical Study Report for Study MS200740-0001

Figure 17. Arithmetic Mean (± Standard Deviation) sIL-6R Observed Serum Concentration-Time Profiles for All Treatments on Linear Scale



LLOQ = lower limit of quantitation, SD = standard deviation, sIL-6R = soluble interleukin-6 receptor
LLOQ = 10.0 µg/L. Individual concentration values below the LLOQ were set to the LLOQ. Predose was the average of the 3 predose samples on Day 1.
Source: Figure 6 in Clinical Study Report for Study MS200740-0001

Figure 18. Mean (±SD) CRP Observed Serum Concentration-Time Profiles for All Treatments on Linear Scale



CRP = C-reactive protein; Lower limit of quantitation (LLOQ) = 0.11 mg/L.
Individual concentration values below the LLOQ were set to LLOQ. Predose is the average of the 3 predose samples on Day 1.

Source: Figure 15.5.1.5 in Clinical Study Report for Study MS200740-0001

Bioanalytical PD Method and Performance

Levels of soluble IL-6R were detected using an ELISA immunoassay based on a Quantikine kit from R&D Systems, and levels of CRP were analyzed using a Roche Modular/immunoturbidimetric platform with a measuring range between 0.1–20 mg/L and a functional sensitivity (LLOQ) of 0.11 mg/L. See Clinical Pharmacology Appendix 14.3.2 for details.

14.3.2. Summary of Bioanalytical Method Validation and Performance

Pharmacokinetics

For the PK similarity study MSB200740-0001, serum MSB11456, US-Actemra, and EU-RoActemra concentrations measured using a validated method (Method TM.2019) were suitable for assessment of PK similarity. Both the method validation entitled “Validation of an Electrochemiluminescence Assay for the Quantitation of Tocilizumab in Human Serum Between 100 and 50000 ng/mL” and sample analysis for the study were performed at (b) (4). In this method, human anti-tocilizumab antibody (HCA252) (Bio-Rad, Puchheim, Germany) coated in 96-well plate was used to capture serum MSB11456, US-Actemra, and EU-Actemra and Ruthenylated human anti-Tocilizumab antibody (HCA253) (b) (4) was used to detect the bound analytes. Table 28 shows the summary of Method TM.2019 method performance in quantification of MSB11456, US-Actemra, and EU-RoActemra during the method validation.

Table 28. Summary of the Bioanalytical Method Validation and In-Study Performance for Measurement of MSB11456, US-Actemra, and EU-RoActemra

Bioanalytical method validation report name, amendments & hyperlinks	Validation of an electrochemiluminescence assay for the quantitation of Tocilizumab biosimilar in human serum Refer to Module 5, Section 5.3.1.4 Reports of bioanalytical and analytical methods for human studies, Report 12095.051118
Method description	The assay employs Meso Scale Discovery (MSD)-based electrochemiluminescence (ECL) to detect and quantitate the amount of Tocilizumab in human serum samples. 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.
Materials used for calibration curve & concentration	**Material:** MSB11456 Batch: TZ1H001 **Concentrations:** 30.9, 103, 258, 1030, 4130, 16500, 65900, 103000,134000 and 155000 ng/mL
Validated assay range	103 ng/mL to 134000 ng/mL
Material used for QC samples & concentration	**Material:** MSB11456 Batch: TZ1H001 Actemra Batches: B1049B03, B3019B02 RoActemra Batch: B1052B03 **Concentrations:** 103, 309, 6600, 101000 and 134000 ng/mL for MSB11456; 100, 300, 6400, 98000 and 130000 ng/mL for Actemra and RoActemra;
MRD	1/10
Source & batch of reagents	**Capture:** Human anti-Tocilizumab antibody (HCA252) – Batch: 1705 and 1710 – Source: Bio-Rad **Detection:** Ruthenylated human anti-Tocilizumab antibody (HCA253) – Batch: 3253.012, 3253.061, 87200 and 89264 – Source: (b) (4) (b) (4)
Regression model & weighting	5-PL curve fitting with $1/y^2$ weighting

Validation parameters	**Method validation summary**			**Source location**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ		8	Refer to Module 5, Section 5.3.1.4 Reports of bioanalytical and analytical methods for human studies, Report 12095.051118, Section 4.3.1
	Cumulative accuracy (%RE):	MSB11456	-4.17% to 3.03%	Report 12095.051118, Table 3
	Cumulative precision (%CV):	MSB11456	≤ 2.61%	
	Cumulative total error (%):	MSB11456	≤ 6.54%	
QC samples performance during inter batch accuracy & precision (LLOQ, QCL, QCM, QCH, ULOQ)	Cumulative accuracy (%RE):	MSB11456	-8.25% to -0.557%	Report 12095.051118, Tables 6 to 11
		Actemra	-12.5% to -6.39%	
		RoActemra	-10.7% to -3.15%	
	Cumulative precision (%CV):	MSB11456	≤ 5.63%	
		Actemra	≤ 4.62%	
		RoActemra	≤ 24.8%	
	Cumulative total error (%):	MSB11456	≤ 13.6%	
		Actemra	≤ 16.3%	
		RoActemra	≤ 28.4%	
Evaluation of automated precision and accuracy on a Hamilton liquid handling system (LLOQ, QCL, QCM, QCH, ULOQ)	Cumulative accuracy (%RE):	MSB11456	-7.73% to 2.22%	Report 12095.051118, Tables 12 to 18
		Actemra	-14.9% to -0.0347%	
		RoActemra	-16.8% to -5.26%	
	Cumulative precision (%CV):	MSB11456	≤ 12.4%	
		Actemra	≤ 12.9%	
		RoActemra	≤ 5.31%	
	Cumulative total error	MSB11456	≤ 17.8%	

	(%):	Actemra	≤ 26.3%	
		RoActemra	≤ 20.1%	
Selectivity & matrix effect in healthy volunteers	No effect observed			Report 12095.051118, Tables 21, 22 and 23.
	Number of batches meeting criteria	MSB11456	10 out of 10	
		Actemra	10 out of 10	
		RoActemra	10 out of 10	
Selectivity & matrix effect in RA samples	No effect observed for MSB11456 and Actemra Matrix effect observed for RoActemra (at LLOQ)			Report 12095.051118, Tables 24 to 34, Appendix F (investigation INV000619).
	Number of batches meeting criteria	MSB11456	9 out of 10 for LLOQ and 10 out of 10 for QCH	
		Actemra	8 out of 10 for LLOQ and 9 out of 10 for QCH after repeat and confirm runs	
		RoActemra	7 out of 10 for LLOQ and 10 out of 10 for QCH after repeat and confirm runs	
Interference & specificity	Not applicable			
Comparison of three sources of Tocilizumab	Number of points in STD curve meeting criteria	Actemra	8 out of 8	Report 12095.051118, Tables 19 and 20.
		RoActemra	8 out of 8	
Hemolysis effect	No effect observed			Report 12095.051118, Tables 35 to 45.
	Number of batches meeting criteria	MSB11456	5 out of 5 after repeat and confirm runs	
		Actemra	5 out of 5 after repeat and confirm runs	
		RoActemra	4 out of 5 after repeat and confirm runs	
Lipemic effect	No effect observed			Report 12095.051118, Tables 46 to 52.
	Number of batches meeting criteria	MSB11456	4 out of 5	
		Actemra	4 out of 5 after repeat and confirm runs	
		RoActemra	4 out of 5 after repeat and confirm runs	
Dilution linearity & hook effect	MSB11456, Actemra and RoActemra: Acceptance criteria met up to 10000-fold dilution No hook effect observed			Report 12095.051118, Tables 53 to 61.
Bench-top/process stability	MSB11456: up to 48 hours at RT. Actemra and RoActemra: up to 20 hours at RT			Report 12095.051118, Tables 62, 63 and 64.
Freeze-thaw stability	MSB11456, Actemra and RoActemra: up to 5 freeze-thaw cycles at -20°C and -80°C			Report 12095.051118, Tables 65 to 70.
Long-term storage	MSB11456, Actemra and RoActemra: up to 44 days at -20°C and -80°C			Report 12095.051118, Tables 71 to 76, and Appendix D.
Parallelism	30 out of 30 samples met criteria			Refer to Module 5, Section 5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports, Study Report MS200740-001, Bioanalytical Report 11924.031218, Table 13
Carry over	Not applicable			

5-PL = 5-parameter logistic, CV = coefficient of variation, ECL = electrochemiluminescence, LLOQ = lower limit of quantification, MRD = minimum required dilution, MSD = meso scale discovery, ULOQ = upper limit of quantification, QC = quality control, QCH = quality control high, QCL = quality control level, QCM = quality control manager, RA = Rheumatoid Arthritis, RE = relative error; R&D = research and development, RT = room temperature.
[a] Total error = |Bias % RE| + Interassay precision % CV.

Source: Table 6 in 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

For studies MS200740-0001, FKS456-001, FKS456-002, and FKS456-003, serum MSB11456, US-Actemra and EU-RoActemra concentrations were determined with a

modified method (TM.2272) at (b) (4). Table 29 below shows the summary of Method TM.2272 method performance in quantification of MSB11456, US-Actemra, and EU-RoActemra during the method validation.

Table 29. Description of Method Modification and Cross-Validation Performance

Bioanalytical method validation report name, amendments &hyperlinks	Validation of an electrochemiluminescence assay for the quantitation of Tocilizumab in human serum between 100 and 50000 ng/mL Refer to Module 5, Section 5.3.1.4 Reports of bioanalytical and analytical methods for human studies, Report 13786.103118.1
Method description	The assay employs Meso Scale Discovery (MSD)-based electrochemiluminescence (ECL) to detect and quantitate the amount of Tocilizumab in human serum samples. Briefly, the high bind 96-well MSD plate is 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.
Materials used for calibration curve & concentration	**Material:** MSB11456 Batch: TZ1H001 **Concentrations:** 100, 250, 500, 2000, 5000, 10000, 40000 and 50000 ng/mL
Validated assay range	100 ng/mL to 50000 ng/mL
Material used for QC samples & concentration	**Material:** MSB11456 Batch: TZ1H001 Actemra Batch: B1049B03 RoActemra Batch: B1052B03 **Concentrations:** 100, 300, 2500, 37000 and 50000 ng/mL for MSB11456, Actemra and RoActemra;
Material used comparability	MSB11456 Batch: TZ1J003, BA056404P Actemra Batch: B2089B06, B2098B03 RoActemra Batch: B3026H12
MRD	1/10
Source & batch of reagents	**Capture:** Human anti-Tocilizumab antibody (HCA252) – Batch: 1705 and 1710 – Source: Bio-Rad **Detection:** Ruthenylated human anti-Tocilizumab antibody (HCA252) – Batch: 3253.012, 3253.061, 87200 and 89264 – Source: (b) (4)
Regression model & weighting	4-PL curve fitting with $1/y^2$ weighting

Validation parameters	Method validation summary			Source location
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ		8	Refer to Module 5, Section 5.3.1.4 Reports of bioanalytical and analytical methods for human studies, Report 13786.103118.1, Section 4.3.1
	Cumulative accuracy (%RE):	MSB11456	-3.00% to 2.00%	Report 13786.103118.1, Table 36
	Cumulative precision (%CV):	MSB11456	≤ 2.98%	
	Cumulative total error (%):	MSB11456	≤ 4.98%	
QC samples performance during accuracy & precision (LLOQ, QCL, QCM, QCH, ULOQ)	Cumulative accuracy (%RE):	MSB11456	-10.6% to -0.695%	Report 13786.103118.1, Tables 6 to 11
		Actemra	-13.7% to 4.50%	
		RoActemra	-10.8% to -3.41%	
	Cumulative precision (%CV):	MSB11456	≤ 9.62%	
		Actemra	≤ 9.25%	
		RoActemra	≤ 8.21%	
	Cumulative total error (%):	MSB11456	≤ 17.4%	
		Actemra	≤ 18.3%	
		RoActemra	≤ 17.0%	
Evaluation of automated precision and accuracy on a Hamilton liquid handling system (LLOQ, QCL, QCM, QCH, ULOQ)	Cumulative accuracy (%RE):	MSB11456	-8.87% to 0.926%	Report 13786.103118.1, Tables 12 to 18
		Actemra	-11.5% to -7.07%	
		RoActemra	-12.2% to -6.22%	
	Cumulative precision (%CV):	MSB11456	≤ 7.01%	
		Actemra	≤ 10.5%	
		RoActemra	≤ 7.40%	
	Cumulative total error (%):	MSB11456	≤ 14.4%	
		Actemra	≤ 17.7%	
		RoActemra	≤ 19.6%	
Selectivity & matrix effect in healthy volunteers	No effect observed			Refer to Module 5, Section 5.3.1.4 Reports of bioanalytical and analytical methods for human studies, Report 13786.103118.1, Tables 20, 21 and 22.
	Number of batches meeting criteria	MSB11456	10 out of 10	
		Actemra	10 out of 10	

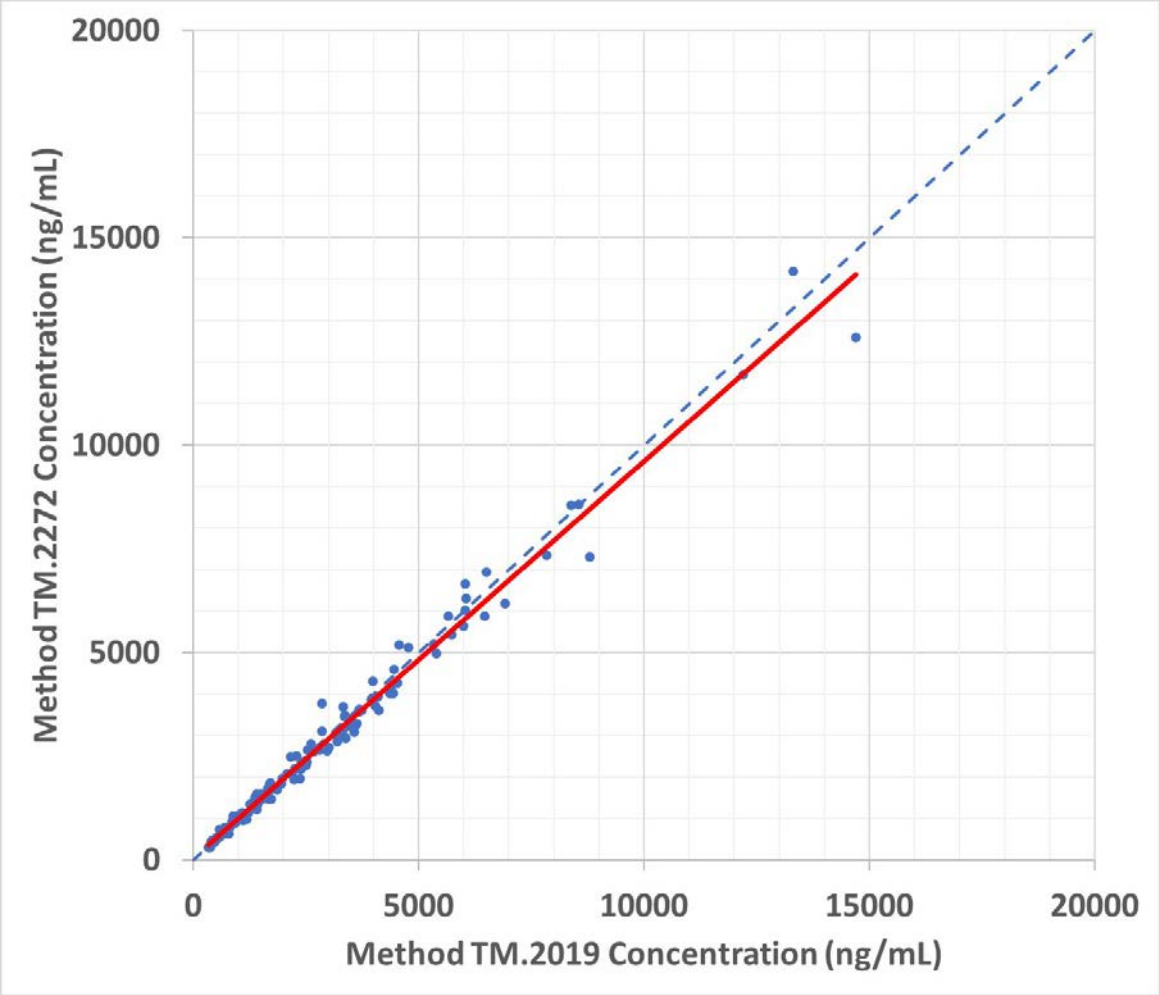
		RoActemra	10 out of 10	
Selectivity & matrix effect in RA samples	No effect observed			Report 13786.103118.1, Tables 23 to 27.
	Number of batches meeting criteria	MSB11456	10 out of 10 after repeat and confirm runs	
		Actemra	9 out of 10	
		RoActemra	10 out of 10	
Interference & specificity	Not applicable			
Comparability of standard curves with Actemra/RoActemra to MSB11456 curve	Number of points in STD curve meeting criteria	Actemra	8 out of 8	Report 13786.103118.1, Table 19.
		RoActemra	8 out of 8	
Hemolysis effect	No effect observed			Report 13786.103118.1, Tables 28, 29 and 30.
	Number of batches meeting criteria	MSB11456	5 out of 5	
		Actemra	5 out of 5	
		RoActemra	5 out of 5	
Lipemic effect	No effect observed			Report 13786.103118.1, Tables 31, 32 and 33.
	Number of batches meeting criteria	MSB11456	4 out of 5	
		Actemra	4 out of 5	
		RoActemra	4 out of 5	
Dilution linearity & hook effect	MSB11456, Actemra and RoActemra: Acceptance criteria met up to 2500-fold dilution No hook effect observed			Report 13786.103118.1, Tables 34, 35 and 36.
Bench-top/process stability	MSB11456, Actemra and RoActemra: up to 27 hours at RT			Report 13786.103118.1, Tables 37, 38 and 39.
Freeze-thaw stability	MSB11456, Actemra and RoActemra: up to 6 freeze-thaw cycles at -20°C and -80°C			Report 13786.103118.1, Tables 40 to 45.
Long-term storage	MSB11456, Actemra and RoActemra: up 451 days at -20°C and -80°C			Report 13786.103118.2, Tables 65 to 70.
Intermediate Solution Stability	MSB11456, Actemra and RoActemra spiked at QCL and QCH in human serum were stable for 20 days at -80°C			Refer to Module 5, Section 5.3.1.4 Reports of bioanalytical and analytical methods for human studies, Report 13786.103118.1, Tables 52, 53 and 54.
Coated Plate Stability	Coated plates stored up to 232 hours at 4°C reliably quantified MSB11456, Actemra and RoActemra at QCL and QCH levels			Report 13786.103118.1, Tables 55, 56 and 57.
MRD Solution Stability	Samples prepared with Hamilton Aliquoting System at LLOQ, QCL, QCM, QCH and ULOQ with MSB11456 and Actemra were stable up to 118 hours when stored at 4°C			Report 13786.103118.1, Tables 58 and 59.
Incurred Sample Reanalysis to bridge TM.2019 and TM.2272	100% of the samples tested were within the ISR acceptance criteria (within 30% of the original result)			Report 13786.103118.1, Table 60.
Parallelism	30 out of 30 samples from MS200740-0001 met criteria			Refer to Module 5, Section 5.3.1.4 Healthy Subject PD and PK/PD Study Reports, Study Report MS200740-001, Bioanalytical Report 11924.031218, Table 13
Comparability Standard curves of Actemra, RoActemra and Biosimilar Phase 3 to Biosimilar IV	Actemra	8 out of 8 Standard Curve points met criteria in 2 runs		Refer to Module 5, Section 5.3.1.4 Reports of bioanalytical and analytical methods for human studies, Report 16611.240820, Table 5
	RoActemra	7 out of 8 Standard Curve points met criteria in 1st run and 8 out of 8 in 2nd run		
	Biosimilar Phase 3	8 out of 8 Standard Curve points met criteria in 2 runs		
ADA interference in Tocilizumab detection	LLOQ	Interference at 25 ng/mL of ADA		Refer to Module 5, Section 5.3.1.4 Reports of bioanalytical and analytical methods for human studies, Report 16611.240820, Tables 6 and 7
	QCH	No detectable interference up to 2000 ng/mL of ADA		
	DQC	No detectable interference up to 2000 ng/mL of ADA		
Carry over	Not applicable			

5-PL = 5-parameter logistic, CV = coefficient of variation, ECL = electrochemiluminescence, LLOQ = lower limit of quantification, MRD = minimum required dilution, MSD = meso scale discovery, ULOQ = upper limit of quantification, QC = quality control, QCH = quality control high, QCL = quality control level, QCM = quality control manager, RA = Rheumatoid Arthritis, RE = relative error; R&D = research and development, RT = room temperature.
[a] Total error = |Bias % RE| + Interassay precision % CV.

Source: Table 8 in 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

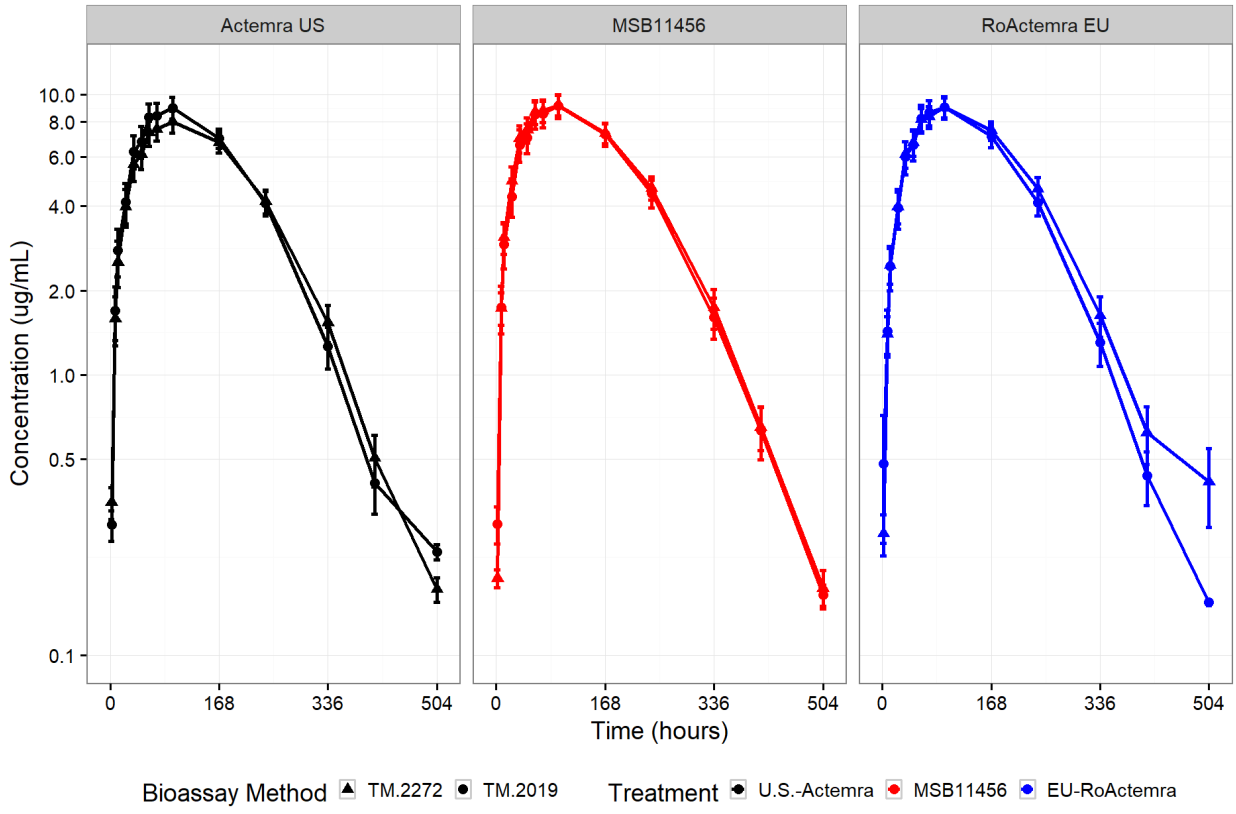
After the initial method (TM.2019) did not meet acceptance criteria during the 3-month long-term stability evaluation, a full validation was conducted for a modified method (TM.2272). During both the method validations, MSB11456, US-Actemra, and EU-RoActemra were used to establish the standard curves, and the accuracy and precision (± 20.0%, ± 25.0% for lower limit of quantitation (LLOQ) and upper limit of quantitation (ULOQ)) was evaluated using MSB11456, US-Actemra, and EU-RoActemra as QC samples. A total of 11572 serum samples were analyzed in Study MS200740-0001. Of which, 5328 samples and 6244 samples were analyzed by method TM.2019 and method TM.2272, respectively. Samples collected from 314 subjects were purely or mainly analyzed by method TM.2019, and samples collected from the other 366 subjects were purely or mainly analyzed by method TM.2722. The Applicant re-analyzed 133 samples, which were originally analyzed by method TM.2019, with method TM.2272 to compare the bioanalytical results between method TM.2019 and method TM.2272. A comparison between the values reported by both two methods showed high consistency (Figure 19). A comparison of concentrations between the two bioassay methods among the three study drugs is depicted in Figure 20. On average, the PK characteristics are consistent between the two bioassay methods. In general, long term stability of serum samples is not expected to be dependent on different bioassay methods. The method validation results supported the use of method TM.2019 in Study MS200740-0001.

Figure 19. Comparison of 133 Serum Samples between Method TM.2019 and TM.2272



Source: Reviewer's analysis based on Table 60. Incurred Sample Reproducibility in Validation Report. 13786.103118

Figure 20. Comparison of Serum Concentration Between Method TM.2019 and TM.2722 Among the Three Study Drugs



Source: Reviewer's analysis

Pharmacodynamics

Levels of soluble IL-6R in Study MS200740-0001 were detected by [redacted] (b) (4) using an ELISA immunoassay based on a Quantikine kit from R&D Systems. See Table 30 for details.

Table 30. Summary Performance of the Bioanalytical Method to Quantify Soluble IL-6R in Serum

Bioanalytical method validation report name, amendments &hyperlinks	Method Qualification for soluble Interleukin 6 receptor (sIL-6R) in Human Serum using Enzyme-Linked Immunosorbent Assay (ELISA) Refer to Module 5, Section 5.3.1.4 Reports of bioanalytical and analytical methods for human studies, Report 8365-584
Method description	The assay employs the quantitative sandwich enzyme immunoassay technique using a commercially available Quantikine ELISA kit from R&D Systems. A monoclonal antibody specific for human IL-6 Rα has been pre-coated onto a microplate. Standards and samples are pipetted into the wells and any IL-6 Rα present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for human IL-6 Rα is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of IL-6 Rα bound in the initial step. The color development is stopped, and the intensity of the color is measured.
Materials used for calibration curve & concentration	**Material:** Recombinant Human IL-6 Rα, Supplier: (b) (4) **Concentrations:** 5.00, 10.0, 25.0, 50.0, 100, 250, 500, 750, 1000 and 1200 ng/mL
Validated assay range	10.0 ng/mL to 1000 ng/mL
Material used for QC samples & concentration	**Material:** Recombinant Human IL-6 Rα, Cat. No.: (b) (4) **Concentrations:** 10 ng/mL, QCL (endogenous [b]), QCM (endogenous [b] + 100 ng/mL), QCH (endogenous [b] + 600 ng/mL), 1000 ng/mL
MRD	1/150
Source & batch of reagents	**Capture:** Plate pre-Coated monoclonal anti-Human IL-6R antibody – Part of Human IL-6R Quantikine ELISA Kit – Source (b) (4) **Detection:** Enzyme-linked polyclonal anti-Human IL-6R antibody - Part# 890115 of Human IL-6R Quantikine ELISA Kit – Source: (b) (4)
Regression model & weighting	5-PL curve fitting with $1/y^2$ weighting

Qualification parameters	**Method qualification summary**			**Source location**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ		8	Refer to Module 5, Section 5.3.1.4 Reports of bioanalytical and analytical methods for human studies, Report 8365-584, Table 1
	Cumulative accuracy (%RE):		-4.3% to 5.6 %	Report 8365-584, Table 1
	Cumulative precision (%CV):		≤ 9.8%	
	Cumulative total error (%):		≤ 10.4%	
QC samples performance during accuracy & precision (LLOQ, QCL, QCM, QCH, ULOQ)	Cumulative accuracy (%RE):		0.2% to 11.9%	Report 8365-584, Table 4
	Cumulative precision (%CV):		≤ 16.2%	
	Cumulative total error (%):		≤ 21.0%	
Selectivity & matrix effect	No effect observed			Report 8365-584, Tables 5, 7 and 8
	Number of batches meeting criteria	Human IL-6R in healthy subjects	10 out of 10 for LLOQ, 8 out of 10 for HQC	
		Human IL-6R in RA subjects	10 out of 10 for LLOQ and HQC after repeat runs	
Interference & specificity	Not applicable			
Hemolysis effect	No effect observed			Report 8365-584, Table 6
	Number of batches meeting criteria		5 out of 5	
	No effect observed			Refer to Module 5, Section 5.3.1.4 Reports of bioanalytical and

Lipemic effect	Number of batches meeting criteria	5 out of 5	analytical methods for human studies, Report 8365-584, Table 6
Dilution linearity & hook effect	Acceptance criteria met up to 640-fold dilution No hook effect observed		Report 8365-584, Table 9
Bench-top/process stability	Human sIL-6R: up to 27.5 hours at RT and up to 70 hours at 4°C.		Report 8365-584, Tables 12 and 13
Freeze-thaw stability	Human sIL-6R: up to 6 freeze-thaw cycles at -80°C		Report 8365-584, Table 11
Long-term stability	Human sIL-6R: stable up to 2 years at -80°C [Kenis, 2002]		Report 8365-584, Table 14
Standard Curve stability in buffer	Standard curve stable for up to 251 days in buffer at -80°C		Report 8365-584, Table 10
Parallelism	5 out of 5 healthy volunteers samples met acceptance criteria. 5 out of 5 RA samples met acceptance criteria		Report 8365-584, Tables 17 and 18
Carry over	Not applicable		
Total sIL-6R Test	Quantikine R&D sIL-6R kit can detect Total sIL-6R (free and bound forms)		Refer to Module 5, Section 5.3.1.4 Reports of bioanalytical and analytical methods for human studies, Report 8365-584, Table 16
Whole Plate Precision	No plate drift or edge effect observed.		Report 8365-584, Table 19
Buffer/Matrix Curve Comparison	Healthy volunteers	No significant difference between Standard curve in buffer and in matrix	Report 8365-584, Figures 1 and 2
	RA samples	No significant difference between Standard curve in buffer and in matrix	

5-PL = 5-parameter logistic, CV = coefficient of variation, ECL = electrochemiluminescence, LLOQ = lower limit of quantification, MRD = minimum required dilution, MSD = meso scale discovery, ULOQ = upper limit of quantification, QC = quality control, QCH = quality control high, QCL = quality control level, QCM = quality control manager, RA = Rheumatoid Arthritis, RE = relative error; R&D = research and development, RT = room temperature.

[a] Total error = |Bias % RE| + Interassay precision % CV.

[b] Endogenous = Normal Human Serum Pool (Lot# 2017-048-8) supplied by (b) (4)

Source: Table 13 in 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

A high sensitivity CRP (hsCRP) assay was used in order to quantify CRP in serum samples from clinical study MS200740-0001. Samples were analyzed using a Roche Modular/immunoturbidimetric platform with a measuring range between 0.1–20 mg/L and a functional sensitivity (LLOQ) of 0.11 mg/L.

14.4. Clinical Appendices

Table 31. TE-SAEs, Extended Period, Weeks 24-55, Safety Population

System Organ Class Preferred Term	MSB11456 N=266 n (%)	EU-RoActemra N=136 n (%)	EU-RoActemra/ MSB11456 N=139 n (%)
Number of Subjects with ≥ 1 TE-SAEs	**20 (7.5)**	**12 (8.8)**	**10 (7.2)**
Infections and Infestations	**18 (6.8)**	**9 (6.6)**	**6 (4.3)**
COVID-19	18 (6.8)	7 (5.1)	5 (3.6)
Arthritis Bacterial	0	1 (0.7)	0
Bacterial Infection	0	0	1 (0.7)
COVID-19 Pneumonia	0	1 (0.7)	0
Pelvic Inflammatory Disease	0	0	1 (0.7)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**1 (0.4)**	**1 (0.7)**	**2 (1.4)**
Benign ovarian tumour	0	0	1 (0.7)
Gastrointestinal stromal tumour	0	0	1 (0.7)
Squamous cell carcinoma of lung	0	1 (0.7)	0
Uterine leiomyoma	1 (0.4)	0	0
Blood and Lymphatic System Disorders	**0**	**2 (1.5)**	**0**
Anaemia	0	1 (0.7)	0
Hilar Lymphadenopathy	0	1 (0.7)	0
Lymphadenopathy Mediastinal	0	1 (0.7)	0
Cardiac Disorders	**0**	**0**	**2 (1.4)**
Arteriosclerosis Coronary Artery	0	0	1 (0.7)
Myocardial Infarction	0	0	1 (0.7)
Gastrointestinal Disorders	**0**	**1 (0.7)**	**1 (0.7)**
Gastrointestinal Haemorrhage	0	1 (0.7)	0
Mechanical Ileus	0	0	1 (0.7)
Reproductive System and Breast Disorders	**2 (0.8)**	**0**	**0**
Menorrhagia	1 (0.4)	0	0
Uterine Polyp	1 (0.4)	0	0
Investigations	**0**	**1 (0.7)**	**0**
SARS-CoV-2 Test Positive	0	1 (0.7)	0
Pregnancy, Puerperium, and Perinatal Conditions	**0**	**0**	**1 (0.7)**
Stillbirth	0	0	1 (0.7)
Respiratory, Thoracic, and Mediastinal Disorders	**0**	**1 (0.7)**	**0**
Bronchiectasis	0	1 (0.7)	0

Source: Adapted from Tables 76, Week 55 Clinical Study Report for Study FKS456-001

Table 32. TEAEs (≥ 2% Incidence), Extended Period, Weeks 24-55, Safety Population

System Organ Class Preferred Term	MSB11456 N=266 n (%)	EU-RoActemra N=136 n (%)	EU-Actemra/ MSB11456 N=139 n (%)
Number of Subjects with ≥ 1 TEAE	**120 (45.1)**	**55 (40.4)**	**57 (41.0)**
Infections and Infestations	**50 (18.8)**	**22 (16.2)**	**19 (13.7)**
COVID-19	18 (6.8)	7 (5.1)	5 (3.6)
Upper respiratory tract infection	11 (4.1)	4 (2.9)	3 (2.2)
Nasopharyngitis	6 (2.3)	4 (2.9)	2 (1.4)
Pharyngitis	0	3 (2.2)	0
Investigations	**31 (11.7)**	**17 (12.5)**	**19 (13.7)**
Alanine Aminotransferase Increased	12 (4.5)	5 (3.7)	5 (3.6)
Blood Bilirubin Unconjugated Increased	2 (0.8)	2 (1.5)	4 (2.9)
Mycobacterium Tuberculosis Complex Test Positive	7 (2.6)	1 (0.7)	0
Blood bilirubin increased	4 (1.5)	0	3 (2.2)
Blood and Lymphatic System Disorders	**20 (7.5)**	**8 (5.9)**	**10 (7.2)**
Leukopenia	10 (3.8)	5 (3.7)	4 (2.9)
Neutropenia	7 (2.6)	2 (1.5)	4 (2.9)
Thrombocytopenia	8 (3.0)	1 (0.7)	0
Anaemia	2 (0.8)	1 (0.7)	3 (2.2)
Metabolism and Nutrition Disorders	**4 (1.5)**	**4 (2.9)**	**5 (3.6)**
Hypercholesterolemia	1 (0.4)	2 (1.5)	3 (2.2)

Source: Adapted from Table 69, Week 55 Clinical Study Report for Study FKS456-001

Table 33. TEAEs Leading to IMP Discontinuation, Extended Period, Weeks 24-55, Safety Population

System organ class Preferred Term	MSB11456 N=266 n (%)	EU-RoActemra N=136 n (%)	EU-Actemra/ MSB11456 N=139 n (%)
Number of Subjects with TEAEs Leading to IMP Discontinuation	**9 (3.4)**	**4 (2.9)**	**10 (7.2)**
Investigations	**6 (2.3)**	**3 (2.2)**	**4 (2.9)**
Blood Bilirubin Unconjugated Increased	2 (0.8)	2 (1.5)	2 (1.4)
Blood Bilirubin Increased	1 (0.4)	0	2 (1.4)
Alanine Aminotransferase Increased	2 (0.8)	0	0
Mycobacterium Tuberculosis Complex Test Positive	1 (0.4)	1 (0.7)	0
General disorders and administration site conditions	**1 (0.4)**	**0**	**2 (1.4)**
Injection Site Erythema	1 (0.4)	0	0
Injection Site Hypersensitivity	0	0	1 (0.7)
Injection Site Pain	1 (0.4)	0	0
Injection Site Pruritus	1 (0.4)	0	0
Injection Site Swelling	1 (0.4)	0	0
Swelling Face	0	0	1 (0.7)
Blood and Lymphatic System Disorders	**1 (0.4)**	**1 (0.7)**	**0**
Hilar Lymphadenopathy	0	1 (0.7)	0
Lymphadenopathy Mediastinal	0	1 (0.7)	0
Thrombocytopenia	1 (0.4)	0	0
Gastrointestinal Disorders	**0**	**0**	**2 (1.4)**
Abdominal Pain	0	0	1 (0.7)
Stomatitis	0	0	1 (0.7)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**0**	**1 (0.7)**	**1 (0.7)**
Benign Ovarian Tumour	0	0	1 (0.7)
Squamous Cell Carcinoma of Lung	0	1 (0.7)	0
Injury, Poisoning and Procedural Complications	**1(0.4)**	**0**	**0**
Limb Injury	1 (0.4)	0	0
Investigations	**0**	**1 (0.7)**	**0**
SARS-CoV-2 Test Positive	0	1 (0.7)	0
Renal and Urinary Disorders	**0**	**0**	**1 (0.7)**
Acute Kidney Injury	0	0	1 (0.7)
Respiratory, Thoracic, and Mediastinal Disorders	**0**	**1 (0.7)**	**0**
Bronchiectasis	0	1 (0.7)	0
Skin and Subcutaneous Tissue Disorders	**0**	**0**	**1 (0.7)**
Pruritus	0	0	1 (0.7)

Source: Adapted from Table 83, Week 55 Clinical Study Report for Study FKS456-001

Table 34. AESIs (≥ 1% Incidence), Extended Period, Weeks 24-55, Safety Population

System Organ Class Preferred Term	MSB11456 N=266 n (%)	EU-RoActemra N=136 n (%)	EU-Actemra/ MSB11456 N=139 n (%)
Number of Subjects with ≥ 1 AESI	**42 (15.8)**	**17 (12.5)**	**21 (15.1)**
Infections and Infestations	**21 (7.9)**	**8 (5.9)**	**8 (5.8)**
COVID-19	12 (4.5)	3 (2.2)	2 (1.4)
Upper Respiratory Tract Infection	3 (1.1)	3 (2.2)	2 (1.4)
Investigations	**8 (3.0)**	**4 (2.9)**	**5 (3.6)**
Blood Bilirubin Unconjugated Increased	2 (0.8)	2 (1.5)	2 (1.4)
Blood Bilirubin Increased	2 (0.8)	0	2 (1.4)
Alanine Aminotransferase Increased	3 (1.1)	0	0
Blood and Lymphatic System Disorders	**5 (1.9)**	**3 (2.2)**	**2 (1.4)**
Leukopenia	3 (1.1)	1 (0.7)	2 (1.4)
Thrombocytopenia	3 (1.1)	1 (0.7)	0

Source: Adapted from Table 87, Week 55 Clinical Study Report for Study FKS456-001

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