Protocol Number: FKS456-001

Official Title: A Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Two-Arm Study to Evaluate the Efficacy, Safety and Immunogenicity of MSB11456 Compared to European Union-approved RoActemra® in Patients with Moderately to Severely Active Rheumatoid Arthritis (APTURA I study)

Document Date: 08 February 2021

NCT Number: NCT04512001

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Protocol Version 3.0 (Global Amendment 2; substantial), dated 01 Feb 2021

Protocol Version 3.2 (Incorporating Global Amendment 2 into Protocol Version 2.2 for the Czech Republic), dated 08 Feb 2021

CLINICAL STUDY PROTOCOL

DRUG:	MSB11456
STUDY NUMBER:	FKS456-001
PROTOCOL TITLE:	A Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Two-Arm Study to Evaluate the Efficacy, Safety and Immunogenicity of MSB11456 Compared to European Union-approved RoActemra® in Patients with Moderately to Severely Active Rheumatoid Arthritis (APTURA I study)
PHASE:	III
IND NUMBER:	IND 129965
EudraCT NUMBER:	2019-004369-42
SPONSOR:	Fresenius Kabi SwissBioSim GmbH Terre Bonne Business Park Route de Crassier 23 – Bâtiment A3 CH – 1262 Eysins Switzerland
SPONSOR MEDICAL LEAD:	[redacted]
VERSION NUMBER/DATE:	Protocol Version 3.0 (Incorporating Global Protocol Amendment 2 - Substantial): 01 February 2021 Protocol Version 2.0 (Incorporating Global Protocol Amendment 1 - Substantial): 06 May 2020 Protocol Version 1.0: 12 February 2020

CLINICAL STUDY PROTOCOL APPROVAL FORM

Protocol Title: A Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Two-Arm Study to Evaluate the Efficacy, Safety and Immunogenicity of MSB11456 Compared to European Union-approved RoActemra® in Patients with Moderately to Severely Active Rheumatoid Arthritis (APTURA I study)

Study No: FKS456-001

Protocol Version No: Version 3.0 Incorporating Global Protocol Amendment 2 - Substantial

Protocol Version Date: 01 February 2021

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the Sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of Good Clinical Practice as described in 21 Code of Federal Regulations parts 50, 54, 56 and 312 and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Name and Title	Approval	Signature	Date
Biometrics: [redacted]	Yes No (circle one)	[redacted]	
Medical Lead: [redacted]	Yes No (circle one)		
Chief Medical Officer: [redacted]	Yes No (circle one)		

FKS456-001

A RANDOMIZED, DOUBLE-BLIND, MULTIPLE-DOSE, PARALLEL-GROUP, TWO-ARM STUDY TO EVALUATE THE EFFICACY, SAFETY AND IMMUNOGENICITY OF MSB11456 TO EUROPEAN UNION-APPROVED ROACTEMRA® IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE RHEUMATOID ARTHRITIS (APTURA I STUDY)

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to MSB11456 are the confidential and proprietary information of Fresenius Kabi SwissBioSim GmbH, and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Fresenius Kabi SwissBioSim GmbH.

I have read the protocol (Version 3.0 dated 01 February 2021), including all appendices and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Council on Harmonisation guidelines and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Fresenius Kabi SwissBioSim GmbH or specified designees. I will discuss the material with them to ensure that they are fully informed about MSB11456 and the study.

My site has implemented risk minimization and the mitigation plan for COVID-19 in line with local regulations and best practices, including precautions such as use of personal protective equipment for patients, site staff and other visitors, site staff health-check and the disinfection of site premises.

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Version 3.0 01 February 2021
Global Protocol Amendment 2 (substantial)
Rationale: Protocol Amendment 2 (substantial) was issued to exclude patients who have received a COVID-19 vaccine from the study until the completion of the Week 30 visit. Due to the lack of data related to potential interference between study treatment and COVID-19 vaccination, COVID-19 vaccination is not allowed from 4 weeks prior to randomization until the completion of the Week 30 visit.
The following changes are incorporated into Version 3.0 of the protocol:

Description of change and rationale for change:
A new exclusion criterion (exclusion criterion #30) was added to exclude patients who have received a COVID-19 vaccine within 4 weeks prior to randomization, are receiving ongoing COVID-19 vaccination at the time of screening or plan to receive COVID-19 vaccination before the completion of the Week 30 visit of the study.
Section(s) of the protocol affected:
Study Summary: Exclusion Criteria and Section 5.3.

Description of change and rationale for change:
A new sentence was added to state that all COVID-19 vaccines administered before the completion of the Week 30 visit will be reported as COVID-19-related protocol deviations.
Section(s) of the protocol affected:
Section 7.16.

Description of change and rationale for change:
A new sentence was added to provide details of the recording of COVID-19 vaccinations on the Concomitant Medication page of the electronic Case Report Form.
Section(s) of the protocol affected:
Section 8.10.

Description of change and rationale for change:
Cross-references to the new COVID-19 vaccination section were added for clarity.
Section(s) of the protocol affected:
Section 8.12.

Description of change and rationale for change:
Inclusion of a new section that provides information for COVID-19 vaccinations.
Section(s) of the protocol affected:
Section 8.13 COVID-19 Vaccinations (new).

Description of change and rationale for change:
Renumbering of Section 8.13 (Management of Specific Adverse Events or Adverse Drug Reactions) and Section 8.14 (Compliance) to Sections 8.14 and 8.15 (respectively) due to the inclusion of a new Section 8.13 (COVID-19 Vaccinations).
Section(s) of the protocol affected:
Section 8.13 (Management of Specific Adverse Events or Adverse Drug Reactions) and Section 8.14 (Compliance).

Description of change and rationale for change:
The study is being conducted in Europe only. Therefore, details regarding North America, Asia and Rest of the World have been removed from the protocol. Details regarding randomization stratification by geographical region and the capping limits for North America have been removed. Details regarding Contract Research Organization's safety reporting in North America have been removed. Details of the Medical Monitor located in North America have been removed.
Section(s) of the protocol affected:
Study Summary: Study Centers, Study Design, Data Analysis and Section 4.1, Section 4.3.1, Section 5.1, Section 7.2, Section 9, Section 12.3, Section 12.5.1, Section 12.5.2 and Appendix I.

Description of change and rationale for change:
The number of countries has been revised from approximately 12 to approximately 10 to account for the study being conducted in Europe only.
Section(s) of the protocol affected:
Study Summary: Study Centers and Section 5.1.

Description of change and rationale for change:
Administrative change updating the name of signatory.
Section(s) of the protocol affected:
Clinical Study Protocol Approval Form.

Description of change and rationale for change:
Inclusion of a reference to Appendix IV to exclusion criterion #1.
Section(s) of the protocol affected:
Section 5.3.

Description of change and rationale for change:
Correction of the reference of Appendix IV to Appendix V.
Section(s) of the protocol affected:
Section 7.10 and Section 7.10.1.3.

Description of change and rationale for change:
Edits to the wording to clarify that the Statistical Analysis Plan will be ready and approved before the Week 30 partial database lock and unblinding.
Section(s) of the protocol affected:
Section 12.5.3.

Description of change and rationale for change:
An update to the date of the RoActemra® EU Summary of Product Characteristics.
Section(s) of the protocol affected:
Section 19.

Description of change and rationale for change:
Update of PIND to IND.
Section(s) of the protocol affected:
Title page and Study Summary.

Description of change and rationale for change:
Minor formatting edits.
Section(s) of the protocol affected:
Throughout the document.

Version 2.0 06 May 2020
Global Protocol Amendment 1 (substantial)
Rationale: Due to the COVID-19 pandemic Global Protocol Amendment 1 (Substantial) was implemented to increase safeguarding measures for the patients.
The following changes are incorporated into Version 2.0 of the protocol:

Description of change and rationale for change:
Inclusion of the statement for the implementation of risk minimization and the mitigation plan for COVID-19 in line with local regulations and best practices, including precautions such as use of personal protective equipment for patients, site staff and other visitors, site staff health-check and the disinfection of site premises.
Section(s) of the protocol affected:
Investigator Confidentiality and Statement Signature Page and Section 6.1.

Description of change and rationale for change:
To inform patients of the nature and impact of COVID-19 on their health, all patients will be provided with a separate Informed Consent Form (containing important information about COVID-19, clinical research study participation and patient consent).
Section(s) of the protocol affected:
Study Summary: Inclusion Criteria, Section 4.5 (Table 1 footnote a), Section 5.2, Section 5.4, Section 7.1 and Section 14.4.

Description of change and rationale for change:
Clarification of exclusion criterion #28 (moved to exclusion criterion #17) stating that if in the opinion of the Investigator the patient is considered for any reason to be an unsuitable candidate for the study the patient will be excluded. In addition, the Investigator should specifically evaluate the patient's eligibility taking into consideration COVID-19 risk factors and situation.
Section(s) of the protocol affected:
Study Summary: Exclusion Criteria and Section 5.3.

Description of change and rationale for change:
Patients with confirmed or suspected active COVID-19 infection are not allowed to participate in the study. A new exclusion criterion was added to reflect this change.
Section(s) of the protocol affected:
Study Summary: Exclusion Criteria and Sections 5.3.

Description of change and rationale for change:
The inclusion that local laboratories are allowed (with pre-approval of the Sponsor) to be used instead of central laboratories if required due to the COVID-19 situation was added.
Section(s) of the protocol affected:
Section 7.12.

Description of change and rationale for change:
The requirement that patients must check their axillary temperature prior to the self-administration of the study drug was added to the protocol. A statement was also added that in the case of an elevated temperature, it is the Investigator's decision to determine any further actions according to local practice and their medical judgment.
Section(s) of the protocol affected:
Study Summary: Study Design, Section 4.1, Section 4.5 (Table 1 Footnote h), Section 7.7 and Section 8.4.

Description of change and rationale for change:
Inclusion of the requirement that body temperature measurement must precede every other assessment.
Section(s) of the protocol affected:
Section 4.5 (Table 1 Footnotes b and h), Section 7.7, Section 7.10 and Section 7.10.2.

Description of change and rationale for change:
Inclusion of a statement for the recording of the time of body temperature into the diary. Instructions are provided to the patients to check their temperature before visiting the clinical site and to contact the site staff immediately in the case that their body temperature is above normal (>37.5°C).
Section(s) of the protocol affected:
Section 8.4.

Description of change and rationale for change:
Details of interruption of study drug due to COVID-19 and re-introduction of study drug based on negative COVID-19 tests or a 2-week symptom-free observation were added.
Section(s) of the protocol affected:
Section 8.6.

Description of change and rationale for change:
Clarification that confirmed COVID-19 cases should be reported as 'otherwise medically important' and accordingly reported as serious adverse events.
Section(s) of the protocol affected:
Section 4.5 Table 1 (new footnote l) and Section 9.2.

Description of change and rationale for change:
A new footnote clarifying that in addition to the inspection of the injection site, the Investigator is also requested to ask the patient during the assessments about any such reaction that may have occurred since the last assessment.
Section(s) of the protocol affected:
Section 4.5 Table 1 (new footnote m).

Description of change and rationale for change:
Removal of text within Section 8.4 describing injection site assessment and reporting. Inclusion of a new section Local Tolerability (Section 7.13) that provides fuller details of injection site reaction assessments and reporting.
Section(s) of the protocol affected:
Section 7.13 (new) and Section 8.4.

Description of change and rationale for change:
Inclusion of Interactive Response Technology to be used in addition to Electronic Data Capture System for screened and randomized patients.
Section(s) of the protocol affected:
Section 5.4.

Description of change and rationale for change:
The section was updated to be compliant with the Contract Research Organization's processes with the inclusion that the Contract Research Organization may also unblind the treatment assignment for the individual patient through the Interactive Response Technology system.
Section(s) of the protocol affected:
Section 8.2.

Description of change and rationale for change:
Removal of the following predefined adverse event of interests: gastrointestinal perforations and serious complications of diverticulitis; CTCAE Grade 3 or higher neutropenia or thrombocytopenia, clinically important symptoms thereof; liver enzyme elevations ≥3 x ULN and/or clinically important elevations in bilirubin elevations, signaling clinically relevant hepatotoxicity; CTCAE Grade 3 or higher elevations in serum lipid levels indicating a materially elevated risk of cardiovascular and cerebrovascular events; active tuberculosis or latent tuberculosis infection). Inclusion of a new statement that any adverse event that leads to interruption of study treatment, permanent discontinuation of study treatment or withdrawal from the study will be considered as a predefined adverse event of interest.
Section(s) of the protocol affected:
Section 10.5.

Description of change and rationale for change:
Removal of the wording of paper as electronic submissions are also accepted. Correction of the responsibilities for E2B reporting. The inclusion of unexpected suspected adverse reaction reporting to Eudravigilance.
Section(s) of the protocol affected:
Section 11.2.

Description of change and rationale for change:
Inclusion of Sponsor's Medical Monitor's details on title page.
Section(s) of the protocol affected:
Title page.

Description of change and rationale for change:
Update of Contract Research Organization's Medical Monitor's details.
Section(s) of the protocol affected:
Appendix I.

Description of change and rationale for change:
Inclusion of study logo into the document header.
Section(s) of the protocol affected:
All sections.

Description of change and rationale for change:
Updates to Table of Contents due to the inclusion of new section; updates to text for abbreviations due to new text; correction of Table 1; update for language consistency; minor formatting updates throughout for consistency.
Section(s) of the protocol affected:
Table of Contents, Section 4.5 (Table 1 footnote m and Table 2), Section 10.2 and throughout the protocol.

Version 1.0 12 February 2020
Initial creation

STUDY SUMMARY

Title:	A Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Two-Arm Study to Evaluate the Efficacy, Safety and Immunogenicity of MSB11456 Compared to European Union-approved RoActemra® in Patients with Moderately to Severely Active Rheumatoid Arthritis (APTURA I study).
IND NUMBER:	IND 129965
EudraCT NUMBER:	2019-004369-42
Rationale:	The purpose of this clinical study is to evaluate the efficacy, safety, immunogenicity, as well as population pharmacokinetics in a sub-study, of MSB11456 a proposed biosimilar to tocilizumab compared to the European Union (EU)-approved RoActemra, in patients with moderately to severely active rheumatoid arthritis who have experienced an inadequate clinical response to at least one disease-modifying anti-rheumatic drug (either synthetic or biologic) and are currently receiving a stable dose of methotrexate. Data from this study combined with the Phase I pharmacokinetic equivalence study MS200740-0001 in healthy volunteers will provide evidence to support similarity between MSB11456 and Actemra®/RoActemra in terms of pharmacokinetics, efficacy, safety, tolerability and immunogenicity.
Study Centers:	It is planned to have approximately 100 study centers in approximately 10 countries (Europe).
Study Period:	The study will have a duration of up to 67 weeks and will include a Screening Period of maximum 28 days prior to first study drug administration, a 24-week Core Treatment Period (Day 1 to Day 169/Week 24), a 28-week Extended Treatment Period (Day 169/Week 24 to Day 365/Week 52), a Safety Follow-Up Visit at Week 55, 4 weeks after the last dose of study drug at Week 51 and a final End of Study Visit will be conducted at Week 63, 12 weeks after the last dose of study drug at Week 51. (Note: The 12-week Safety Evaluation starts at Week 51, after the last study drug injection and the Extended Treatment Period ends at Week 52.) The end of the study

will be the date when the last patient has completed the last study assessment.

Target Population: Male or female patients aged ≥18 years old with moderately to severely active rheumatoid arthritis despite therapy with at least one disease-modifying anti-rheumatic drug (either synthetic or biologic) and who are receiving a stable dose of methotrexate.

Inclusion Criteria: Male and female patients with moderately to severely active rheumatoid arthritis who:

1. Are ≥18 years of age.
2. Have a body weight of <100 kg at screening.
3. Diagnosis of rheumatoid arthritis according to the revised 1987 American College of Rheumatology (ACR)/European League Against Rheumatism Classification 2010 criteria with disease duration of ≥6 months prior to the Screening Visit.
4. Have moderately to severely active rheumatoid arthritis as defined by:
   a. Swollen Joint Count ≥6 (66 joint count) and Tender Joint Count ≥6 (68 joint count) at screening and randomization.
   b. Radiographic evidence of ≥1 joint with a definite erosion attributable to rheumatoid arthritis at screening. The radiographic evidence of joint erosion should be no older than 6 months.
   c. C-reactive protein ≥1 mg/dL (≥10 mg/L) and/or erythrocyte sedimentation rate ≥28 mm/hour at screening.
5. Must have been treated with methotrexate for at least 12 consecutive weeks immediately prior to randomization and are on a stable dose between 10 and 25 mg/week methotrexate for the last 8 weeks prior to screening. Note: Oral and/or subcutaneous administration of methotrexate is allowed.
6. Must be willing to receive at least 5 mg/week or equivalent of folic acid.
7. Have had previous inadequate clinical response to at least one disease-modifying anti-rheumatic drug (either synthetic or biologic).

8. Have withdrawn all disease-modifying anti-rheumatic drugs other than methotrexate at least 8 weeks prior to randomization with the exception of leflunomide which must have been discontinued for ≥12 weeks prior to randomization (or ≥4 weeks after 11 days of standard cholestyramine washout).

9. Had discontinued biologic treatment for ≥12 weeks prior to randomization. Note: The population of patients with previous exposure to any biologic treatment will be capped at 10% of the total study population.

10. Must be able and willing to self-administer subcutaneous injections or have a qualified/trained person(s) available to administer subcutaneous injections.

11. Women of childbearing potential (i.e., considered fertile following menarche and until becoming postmenopausal unless permanently sterile) can participate only if they have a negative serum pregnancy test at screening and a negative urine pregnancy test at Day -1 before randomization. Women of childbearing potential must have used and agree to use a highly effective contraception (i.e., methods with a failure rate of less than 1% per year) for 4 weeks before randomization and must agree to continue to practice adequate contraception for 3 months after the last study drug administration.

    Women of childbearing potential whose preferred lifestyle is total abstinence from intercourse may participate in the study.

    Withdrawal and rhythm methods are not considered to be highly effective methods of contraception and are not permitted as the sole method of contraception in this study.

12. Women who are postmenopausal (i.e., age-related amenorrhea ≥12 consecutive months and increased follicle-stimulating hormone >40 mIU/mL), or women who have undergone documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, a follicle-stimulating hormone sample will be tested at screening.

Females on hormone replacement therapy and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their hormone replacement therapy during the study. Otherwise, they must discontinue hormone replacement therapy to allow confirmation of postmenopausal status before study enrollment. Women who were taking hormone replacement therapy prior to study entry are allowed to participate in the study if they have a negative pregnancy test at screening and prior to randomization. Initiating hormone replacement therapy during the study is not permitted.

13. Men must either be surgically sterile (vasectomy with documented confirmation of aspermia) or must agree to use a condom (with spermicide) and to have their female partners agree to use a highly effective contraception (i.e., methods with a failure rate of less than 1% per year), unless their partners are infertile or surgically sterile, from the time of the first administration of study drug and for at least 3 months after the study drug administration and refrain from donating sperm during this period.

14. Must voluntarily give written informed consent before any study-related activities are performed. Patients must read and fully understand the Informed Consent Form and the requirements of the study. Patients must be willing to comply with all study visits and assessments. Patients must be willing to complete each study procedure. Note: A separate Informed Consent Form (containing important information about COVID-19, clinical research study participation and patient consent) will be provided to and signed by each patient to provide information on the general risks of study participation related to COVID-19 and to document that it is understood by the patient. Another separate Informed Consent Form will be required to be understood and signed by partners of male participating patients who become pregnant during the study or within 10 weeks after the participating patient's last dose of study drug.

Exclusion Criteria:

Patients will be excluded from the study if any of the following criteria are met:

1. American College of Rheumatology functional class IV as defined by the ACR classification of functional status or wheelchair/bedbound.

2. Rheumatic autoimmune disease or history of/current inflammatory joint disease other than rheumatoid arthritis or significant systemic involvement secondary to rheumatoid arthritis (e.g., Felty's syndrome, vasculitis, pulmonary fibrosis, gout, Lyme disease, psoriatic arthritis). Sjögren's syndrome secondary to rheumatoid arthritis is allowed.

3. Previously received tocilizumab, an investigational or licensed biosimilar of tocilizumab or any interleukin-6 acting drugs (approved or investigational).

4. Prior use of targeted synthetic disease-modifying anti-rheumatic drugs like janus kinase inhibitors (approved e.g., tofacitinib, baricitinib, upadacitinib or investigational e.g., filgotinib, peficitinib).

5. Prior use of any biological agent for a condition other than rheumatoid arthritis (e.g., ranibizumab, denosumab).

6. Prior use of more than two biologic treatments for rheumatoid arthritis.

7. Prior use of biologic investigational drugs (excluding biosimilars) for the treatment of rheumatoid arthritis.

8. Received any investigational drugs within 12 weeks or five drug half-lives (whichever is longer) prior to screening or planned intake of an investigational drug during the course of this trial including the Follow-Up Period.

9. 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 has previously undergone total lymphoid irradiation.

10. Use of non-steroidal anti-inflammatory drugs not at a stable dose for at least 4 weeks prior to randomization or exceeding the maximum recommended dose. Note: Patients are permitted to take aspirin at a dose of ≤325 mg daily for cardiac prophylaxis. Use of paracetamol is allowed in the study.

11. Use of oral corticosteroids >10 mg/day prednisone or equivalent if the dose has not been stable for at least 6 weeks prior to randomization.

12. Intra-articular or parenteral corticosteroids within 4 weeks prior to randomization.

13. Use of high potency opioid analgesics (e.g., hydromorphone, oxycodone, fentanyl, or morphine).

14. Has been treated with intravenous gamma globulin or plasmapheresis within 6 months of randomization.

15. Received a live or attenuated vaccine within 4 weeks prior to randomization.

16. History of hypersensitivity or severe allergic reactions to monoclonal antibodies, any components of the study drug formulations, comparable drugs, or latex.

17. Patient is considered by the Investigator, for any reason, to be an unsuitable candidate for the study. Investigator should specifically evaluate the patient's eligibility taking into consideration COVID-19 risk factors and situation.

18. Has a serious and/or unstable and/or poorly controlled medical condition such as but not limited to poorly controlled diabetes, unstable ischemic heart disease, uncontrolled hypertension (systolic ≥160 mmHg and/or diastolic ≥95 mmHg) or other cardiovascular, cerebrovascular, gastrointestinal, hepatic, renal, hematological (including pancytopenia, aplastic anemia, or blood dyscrasia), endocrine, nervous system or pulmonary disease or other relevant medical condition or a history of clinically significant disease or any other condition that, in the opinion of the Investigator, would put the patient at risk by participation in the study.

19. History of diverticulosis requiring antibiotic treatment or any other gastrointestinal condition (e.g., inflammatory bowel disease, mechanic bowel obstruction, hernia) that might predispose the patient to gastrointestinal perforations.

20. Uncontrolled medical conditions (e.g., asthma, psoriasis) for which flares are commonly treated with corticosteroids or systemic corticosteroid treatment for these conditions within the last 12 months prior to randomization.

21. Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery during the study.

22. History of, or current myeloproliferative or lymphoproliferative disease or malignancy. Curatively treated basal or squamous cell carcinoma of the skin is not excluded, unless it occurred within 12 months of randomization. Curatively treated localized in situ carcinoma of the cervix within 5 years of randomization is also not excluded, if there is no evidence of recurrence prior to randomization.

23. Medical evidence of current or history of primary or secondary immunodeficiency as per Investigator's judgment.

24. Pre-existing or recent-onset central or peripheral nervous system demyelinating disorder, such as multiple sclerosis or optic neuritis, or symptoms suggestive of such a disorder as per Investigator's judgment.

25. Confirmed or, based on the signs and symptoms observed at the time of assessment, suspected active COVID-19 infection at the time of screening and/or randomization.

26. Has had any infection as follows:

    a. Herpes zoster or any opportunistic invasive infection (e.g., histoplasmosis, coccidioidomycosis, blastomycosis, pneumocystis, listeriosis, legionellosis, or parasitic infestations) within 6 months of screening.

b. Frequent (more than three of the same type of infection per year requiring treatment) chronic or recurrent infections (e.g., urinary tract or upper respiratory tract infections).

c. A positive test for human immunodeficiency virus subtype 1 or 2, hepatitis C antibody, hepatitis B surface antigen and/or core antibody for immunoglobulin G and/or immunoglobulin M or total immunoglobulin at screening.

d. A serious infection defined as requiring hospitalization or treatment with intravenous antibiotics within 8 weeks prior to randomization.

e. Required treatment with oral antibiotics and/or anti-fungal drugs within 14 days prior to randomization.

27. Medical evidence of active or latent tuberculosis as indicated by a positive QuantiFERON®-TB Gold Plus test, chest X-ray and/or clinical examination or has had active or latent tuberculosis disease at any time in the past.

Patients will be screened for latent tuberculosis infection by the QuantiFERON®-TB Gold Plus test and by chest X-ray. Note: If a bidirectional chest X-ray is available within the 3 months before randomization, the X-ray will not be required to be repeated at screening. If a patient tests positive for latent tuberculosis infection at screening, the patient will fail screening and will not be eligible for participation in the study.

If the QuantiFERON®-TB Gold Plus test is indeterminate, patients may be retested once within the Screening Period:

a. If the retest is negative, the patient is eligible to participate in the study.

b. If the retest is positive, the patient is not eligible to participate in the study.

c. If the retest is again indeterminate, the patient is considered as having latent tuberculosis infection and is not eligible to further participate in the study. No further QuantiFERON®-TB Gold Plus testing will be performed.

28. History of clinically significant drug or alcohol abuse within the last year prior to randomization.

29. Laboratory abnormalities (excluding erythrocyte sedimentation and C-reactive protein values) that were considered clinically significant by the Investigator OR any of the following at screening:

a. Hemoglobin <8 g/dL for women or 8.5 g/ dL for men.

b. White blood cells $<3.5 \times 10^9$/L.

c. Absolute neutrophil count $<2.0 \times 10^9$/L.

d. Platelet count $<100 \times 10^9$/L.

e. Alanine aminotransferase or aspartate aminotransferase >1.5 times the upper limit of normal.

f. Creatinine >1.5 mg/dL if the patient is aged <65 years old, or >upper limit of normal if the patient is aged ≥65 years old or proteinuria ≥3+ by dipstick.

g. Creatinine clearance <50 mL/min (Cockcroft-Gault formula).

30. Received a COVID-19 vaccine within 4 weeks prior to randomization, are receiving ongoing COVID-19 vaccination at the time of screening or plan to receive COVID-19 vaccination before the completion of the Week 30 visit of the study. COVID-19 vaccination is considered ongoing if a multidose regimen has been started but has not been completed.

Number of Patients: A total of 542 patients (271 per treatment arm) are planned to be randomized at Day 1.

Primary, Secondary and Exploratory Objectives:

Primary:

- To demonstrate equivalent efficacy of proposed biosimilar tocilizumab MSB11456 and EU-approved RoActemra both administered subcutaneously to patients with moderately to severely active rheumatoid arthritis.

Secondary:

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

Exploratory:

- To explore the effects of a single treatment transition (i.e., in patients who transitioned from EU-approved RoActemra to MSB11456) on efficacy, safety and immunogenicity.

- To describe pharmacokinetic parameters of MSB11456 and RoActemra.

Study Design: This is a multicenter, randomized (1:1), active-controlled, double-blind, multiple fixed-dose, multinational, two-arm, parallel-group study to compare the efficacy, safety and immunogenicity of the proposed biosimilar candidate MSB11456 versus EU-approved RoActemra in patients with moderately to severely active rheumatoid arthritis. In a

sub-study, the population pharmacokinetic of MSB11456 will be compared with the population pharmacokinetic profile of EU-approved RoActemra during the 52-week treatment period.

This study will enroll patients with moderately to severely active rheumatoid arthritis who have an inadequate response to ≥1 disease-modifying anti-rheumatic drug(s) which may include biologic disease-modifying anti-rheumatic drugs and who are currently receiving a stable dose of methotrexate. Patients who have previously received one or two biologic treatments in total for rheumatoid arthritis may be allowed to participate in the study. However, the population of patients with previous exposure to any biologic treatment will be capped at 10% of the total study population. Patients who have previously received more than two biologic treatments for rheumatoid arthritis will not be permitted to participate in the study.

Patients must have received methotrexate for at least 12 consecutive weeks immediately prior to randomization and are on a stable dose between 10 and 25 mg/week methotrexate for the last 8 weeks prior to screening. Patients will continue to take the same stable dose of methotrexate during the 52-week treatment period of the study. All other disease-modifying anti-rheumatic drugs must be withdrawn prior to randomization.

The study will have a duration of up to 67 weeks and will include a Screening Period of maximum 28 days prior to first study drug administration, a double-blind 24-week Core Treatment Period (Day 1 to Day 169/Week 24), an additional 28-week double-blind Extended Treatment Period (Day 169/Week 24 to Day 365/Week 52) and a 12-week Safety Follow-Up Period. A Safety Follow-Up Visit will be performed at Week 55, 4 weeks after the last dose of study drug at Week 51 and a final End of Study Visit will be conducted at Week 63, 12 weeks after the last dose of study drug at Week 51. (Note: The 12-week Safety Evaluation starts at Week 51, after the last study drug injection and the Extended Treatment Period ends at Week 52.) The end of the study for each patient is defined as the patient's last visit.

Patients whose eligibility is confirmed at baseline will be randomized in a 1:1 ratio by an Interactive Response Technology system to receive either MSB11456 or the EU-approved RoActemra at a dose of 162 mg delivered by subcutaneous injection starting at Day 1, then weekly up to Week 51 inclusive. Randomization will be stratified by previous

exposure to biologic treatment for rheumatoid arthritis (yes/no). The first three doses of study drug (162 mg at Day 1, Day 8 and Day 15) will be administered on-site to ensure the patient or their caregiver is appropriately trained. Patients will be monitored for 2 hours following these first three doses of study drug. The following weekly doses of study drug can be self-administered if the patient is able to self-administer him/herself at the discretion of the Investigator. Patients will check their axillary temperature prior to the self-administration of study drug. In the case of an elevated temperature, it is the Investigator's decision to determine any further actions according to local practice and their medical judgment.

The primary efficacy endpoint will be evaluated and reported at Week 24 (7 days after the 24th study drug administration) after all patients have completed the Week 30 assessments, or have terminated the study before Week 30.

At Week 24, after all efficacy and safety assessments have been performed, patients will enter the Extended Treatment Period. Patients who were originally randomized to receive RoActemra will be re-randomized in a 1:1 ratio to continue their weekly treatment with RoActemra or to switch to MSB11456 starting at Week 24. Patients who were originally randomized to MSB11456 will continue this treatment for the complete 52 weeks of study treatment. During the Extended Treatment Period, efficacy, safety and immunogenicity data will be analyzed up to Week 52 with the last assessment performed 7 days after the last study drug administration (i.e., on Week 51).

Two safety visits are planned after the Extended Treatment Period (Day 169/Week 24 to Day 365/Week 52), the first at Week 55 (Safety Follow-Up) (4 weeks after the last dose of study drug at Week 51) and a second at Week 63 (End of Study Visit) (12 weeks after the last dose of study drug at Week 51). No prohibited treatment for rheumatoid arthritis (as defined in the protocol) is permitted during the month following the last dose of study drug (i.e., Weeks 51 to 55) to allow for the collection of safety data.

Safety data will be collected and analyzed at Weeks 55 and 63 (i.e., 4 and 12 weeks after the last study drug administration, respectively). Samples for immunogenicity analysis will be collected at Week 55.

Patients that received at least one dose of study drug in either the 24-week Core Treatment Period or the Extended Treatment Period and are permanently discontinued from study drug before the end of that period will be encouraged to remain in the study and attend all study visits of the period of discontinuation, irrespective of when they received the last study drug dose, to collect as much safety and efficacy data as possible. If a patient discontinues study drug prior to Week 24, the patient will remain in the study up to the completion of the Week 24 assessments to allow for the collection of efficacy, safety and immunogenicity data for the assessment of similarity for a full 24-week period before switching occurs. Patients who discontinue study drug before or at Week 24 will not be re-randomized at Week 24 and will discontinue the study. If a patient discontinues study drug during the Extended Treatment Period, the patient will be followed-up until the End of Study Visit.

Patients that discontinue study drug prematurely should be followed for at least 4 weeks after the last study drug dose and either complete a 4-week Safety Follow-Up Visit or have the corresponding assessments completed at a suitable scheduled visit.

Patients that permanently discontinue study drug should not receive any prohibited medications (as defined in the protocol) until the completion of the 4-week Safety Follow-Up assessments.

Pharmacokinetic trough concentration samples will be collected from all study patients at scheduled visits.

Patients may be asked to participate in a population pharmacokinetic sub-study performed during the 24-week Core Treatment Period (Day 1 to Day 169/Week 24) and contribute additional pharmacokinetic samples. Participation in the population pharmacokinetic sub-study is optional. Eight additional post-dose pharmacokinetic samples will be collected in each of the patients included in a pharmacokinetic subset of up to approximately 60 patients (approximately 30 from both arms) to enable a population pharmacokinetic model of tocilizumab concentration-time course in rheumatoid arthritis patients.

Schedule of Visits and Assessments:

Patients will be screened for eligibility between Day -28 to Day -1 (screening). Informed consent will be obtained before performing any study-related procedures.

	Baseline assessments and thereafter randomization and first study drug administration will be at Day 1 (baseline). Patients will attend visits at site on Weeks 1, 2, 4, 8, 12, 16, 24, 30, 42 and 52. For patients that complete the full 51 week observation period follow-up visits for safety assessments will be performed 4 weeks (Week 55) and 12 weeks (Week 63) after the last study drug administration. In addition to the site visits, administrations performed at home will be recorded in a diary with the accurate dosing information (dosing date and time).
Investigational Medicinal Product: **Dose/Mode of Administration /Dosing Schedule**	MSB11456 at a dose of 162 mg administered subcutaneously every week. Each dose to be individually packed and to contain 162 mg/0.9 mL solution for injection in pre-filled syringe.
Reference Therapy: **Dose/Mode of Administration /dosing Schedule**	EU-approved RoActemra at a dose of 162 mg administered subcutaneously every week. Each dose to be individually packed and to contain 162 mg/0.9 mL solution for injection in pre-filled syringe.
Planned Treatment Duration Per Patient:	Patients will receive 52 weekly study drug administrations.
Primary Endpoint:	The primary efficacy endpoint is the mean absolute change from baseline in Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR) at Week 24.
Secondary Endpoints:	**Efficacy:** • DAS28-ESR mean absolute change from baseline at all assessment visits (except Week 1) (i.e., at Weeks 2, 4, 8, 12, 16, 30, 42 and 52) other than Week 24.

- ACR20 (20% improvement in ACR Core Set Measurements) response rate at Week 24.

Safety:

- Occurrence of treatment-emergent adverse events up to Week 24, Week 30, Week 55 and Week 63.
- Occurrence of serious adverse events up to Week 24, Week 30, Week 55 and Week 63.

Immunogenicity:

- Antidrug antibody incidence at Weeks 2, 12, 24, 30, 52 and 55.
- Antidrug antibody titer at Weeks 2, 12, 24, 30, 52 and 55.
- Neutralizing antibody incidence at Weeks 2, 12, 24, 30, 52 and 55.

Other Endpoints:

Efficacy:

- Disease Activity Score 28-C-Reactive Protein (DAS28-CRP) mean change from baseline at all assessment visits (except Week 1) (i.e., at Weeks 2, 4, 8, 12, 16, 24, 30, 42 and 52).
- ACR20 response rates at all assessment visits (except Week 1) other than Week 24.
- ACR50/70 (50% and 70% improvement in ACR Core Set Measurements) response rates at all assessment visits (except Week 1).
- Proportion of patients with DAS28-ESR and DAS28-CRP categorical responses (remission, Low Disease Activity and ACR/European League Against Rheumatism criteria (Boolean-based) responses categories) at all assessment visits (except Week 1).
- Clinical Disease Activity Index and Simplified Disease Activity Index changes from baseline and categories (i.e., remission and Low Disease Activity) at all assessment visits (except Week 1).

Safety:

- Changes in vital signs, clinical laboratory values (hematology, clinical chemistry, urinalysis), abnormalities in 12-lead electrocardiogram and physical examination up to Week 24, Week 30, Week 55 and Week 63.

Exploratory Endpoints:

Pharmacokinetic Endpoints:

- Trough concentration.
- Model-based pharmacokinetic parameters (including, but not limited to, predicted maximum plasma concentration and area under the concentration-time curve) using a population pharmacokinetic model.

Statistical Methods:

Equivalence Margins:

Primary Efficacy Endpoint DAS28-ESR at Week 24:

- For the Food and Drug Administration (FDA), the equivalence margins are set to [-0.6, 0.5].
- For the European Medicines Agency (EMA), the equivalence margins are set to ±0.6.

Secondary Efficacy Endpoint ACR 20 at Week 24:

- The equivalence margins are set to ±15%.

Sample Size:

A sample size of 542 randomized patients (271 patients per arm) is chosen to provide approximately 460 patients (230 per arm) in the Per Protocol analysis set at Week 24, assuming a 15% drop-out rate (including major protocol deviations).

For the FDA:

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

For the EMA:

A total of 460 evaluable patients (230 per arm) will provide 90% power to demonstrate equivalence between treatments for the primary endpoint, with equivalence margins of ±0.6 and a type I error of 2.5%, assuming no difference between the two treatment groups and a common standard deviation of 1.76.

In addition, this sample size provides more than 80% power to demonstrate that the 95% confidence interval for the difference between treatments in the secondary efficacy endpoint ACR20 response rate at Week 24 will be included in the equivalence interval [-15%, +15%], assuming no difference between the two treatment

groups and that both MSB11456 and tocilizumab have an ACR20 response rate of 60% at Week 24.

Data Analysis

Change from baseline at Week 24 in DAS28-ESR will be analyzed using an analysis of covariance with study drug, and previous exposure to biologic treatment for rheumatoid arthritis (yes/no) strata as fixed effects and baseline DAS28-ESR as a covariate. The difference between treatments will be estimated by the least squares mean difference between MSB11456 and tocilizumab, with its 95% confidence interval for the EMA and its 90% confidence interval for the FDA.

- For the FDA: MSB11456 will be considered equivalent to tocilizumab if the 90% confidence interval for the difference in mean change from baseline to Week 24 in DAS28-ESR between MSB11456 and tocilizumab lies entirely within the equivalence interval of [-0.6, 0.5] in the Intent-To-Treat Analysis Set. The analysis will be repeated for the Per Protocol Analysis Set.

- For the EMA: MSB11456 will be considered equivalent to tocilizumab if the 95% confidence interval for the difference in mean change from baseline to Week 24 in DAS28-ESR between MSB11456 and tocilizumab lies entirely within the equivalence interval of [-0.6, 0.6] in the Intent-To-Treat Analysis Set. The analysis will be repeated for the Per Protocol Analysis Set.

Patients who discontinue treatment before Week 24 (Core Treatment Period) will be asked to return for all planned assessments visits of the Core Treatment Period. All available values will be used in the analysis, including the DAS28-ESR values of the patients who discontinued treatment before Week 24, but completed Week 24 Visit efficacy assessments (as requested in the study). The details of the data imputation rules will be provided in the Statistical Analysis Plan.

All secondary efficacy endpoints will be analyzed on the Intent-To-Treat and Per Protocol Analysis Sets.

The response rates will be compared using 95% stratified (on previous exposure to biologic treatment) Newcombe confidence intervals for the difference. For the analysis of longitudinal continuous data, mixed-effect repeated measure models will be employed. The fixed

effects of treatment, visit, treatment-by-visit-interaction and stratification factors will be included in the model and the 95% confidence interval for the least-squared mean at each time point will be provided.

For time to event variables, results will be summarized by means of Kaplan-Meier curves together with a summary of associated statistics (median, confidence interval) and the number of patients at risk.

Descriptive summary statistics will be provided throughout.

Safety and immunogenicity data will be listed and summarized using appropriate descriptive statistics on the Safety Analysis Set.

Descriptive statistics will be provided for results of the pharmacokinetic exploratory analyses.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

28SJC	28–Swollen Joint Count (abbreviation used in equations only)
28TJC	28–Tender Joint Count (abbreviation used in equations only)
ACR	American College of Rheumatology
ACR20	20% Improvement in ACR Core Set Measurements
ACR50	50% Improvement in ACR Core Set Measurements
ACR70	70% Improvement in ACR Core Set Measurements
$AUC_{0\text{-inf}}$	Area Under the Concentration-Time Curve From Time 0 Extrapolated to Infinity
$AUC_{0\text{-last}}$	Area Under the Plasma Drug Concentration-Time Curve Up to the Last Quantifiable Time Point
CDAI	Clinical Disease Activity Index
C_{max}	Maximum Plasma Concentration
CRP	C-Reactive Protein (abbreviation used in equations only)
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
D	Day (abbreviation used in tables only)
DAS28	Disease Activity Score-28 Joint Count
DAS28-CRP	Disease Activity Score-28 C-Reactive Protein
DAS28-ESR	Disease Activity Score-28 Erythrocyte Sedimentation Rate
EMA	European Medicines Agency
EOT	End of Treatment (abbreviation used in tables only)

ESR	Erythrocyte Sedimentation Rate (abbreviation used in equations only)
ET	Early Termination (abbreviation used in tables only)
EU	European Union
EU-RMP	European Union-Approved Reference Medicinal Product (abbreviation used in figure only)
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FU	Follow-Up (abbreviation used in figure only)
GCP	Good Clinical Practice
GH	General Health (abbreviation used in equation only)
HIV-1	Human Immunodeficiency Virus Subtype 1
HIV-2	Human Immunodeficiency Virus Subtype 2
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
MDGA	Physician's Global Assessment of Disease Activity (abbreviation used in equations only)
MedDRA	Medical Dictionary for Regulatory Activities
Mil-6R	Membrane-Bound Human Interleukin-6 Receptor
MTX	Methotrexate (abbreviation used in figure only)
n.a.	not applicable (abbreviation used in tables only)
NCI	National Cancer Institute

PGA	Patient's Global Assessment of Disease Activity (abbreviation used in equations only)
SDAI	Simplified Disease Activity Index
SJC28	28-Swollen Joint Count (abbreviation used in equations only)
Sil-6R	Soluble-Bound Human Interleukin-6 Receptor
TJC28	28-Tender Joint Count (abbreviation used in equations only)
ULN	Upper Limit of Normal
US	United States
W/wk	Week (abbreviation used in tables only)

1 INTRODUCTION AND RATIONALE

1.1 Background

Tocilizumab is a recombinant humanized monoclonal immunoglobulin subtype G1 antibody that binds to both soluble- and membrane-bound human interleukin-6 receptors (Sil-6R and Mil-6R) thereby inhibiting Sil-6R- and Mil-6R-mediated signaling. Interleukin-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-lymphocytes, monocytes and fibroblasts. Interleukin-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of hematopoiesis and has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis and neoplasia [1].

Tocilizumab is approved for the treatment of adult patients with moderate to severely active rheumatoid arthritis under two different pharmaceutical forms: concentrate for solution for infusion (intravenous use) and for injection in pre-filled syringe (subcutaneous use). Both are marketed as RoActemra (Europe) or Actemra (United States, US), Roche/Genentech. Tocilizumab can be used alone or with methotrexate or other conventional disease-modifying anti-rheumatic drugs in adult rheumatoid arthritis patients who are intolerant to, or have failed to respond to, other anti-rheumatic medications.

Tocilizumab is also approved for: treatment of giant cell arteritis (subcutaneous only; European Union [EU]/US), polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis (subcutaneous/intravenous; EU/US), cytokine release syndrome in adult and pediatric patients (intravenous only; EU/US), and in addition in adult patients with severe, active and progressive rheumatoid arthritis who previously have not been treated with methotrexate (intravenous/subcutaneous; EU only).

MSB11456 is being developed as a biosimilar to RoActemra (tocilizumab), solution for injection in pre-filled syringe (subcutaneous use). The dosing regimen will be 162 mg administered subcutaneously once every week.

1.2 Benefit-Risk

MSB11456 shows structural and functional concordance with the reference products, US-licensed Actemra and EU-approved RoActemra, pointing towards a commonality of benefits and risks between MSB11456 and the reference products. Minor variations in the safety profile between MSB11456 and the reference products cannot be excluded due to subtle differences in their molecular structure. If these are to become clinically noticeable, they are most likely to manifest in the form of signs and symptoms of hypersensitivity as a consequence of the discriminatory ability of the immune system.

Because of their subtlety, however, pronounced deviations from the safety profile of the reference products are not expected. Signs and symptoms of hypersensitivity have been classified as adverse event of special interest and will be closely monitored during all clinical investigations with MSB11456.

In conclusion, the overall benefit-risk balance for MSB11456 is expected to be favorable based on the demonstrated structural and in vitro functional similarity with the US-licensed Actemra and EU-approved RoActemra. Investigators should consider the known risks for the reference products as equally applicable for MSB11456. Slight differences in the safety profile cannot be ruled out (both unfavorable and favorable) and will be monitored in the clinical investigations.

1.3 Study Rationale

The purpose of this clinical study is to evaluate the efficacy, safety, immunogenicity as well as population pharmacokinetics in a sub-study of MSB11456 a proposed biosimilar to tocilizumab compared to the EU-approved RoActemra, in patients with moderately to severely active rheumatoid arthritis who have experienced an inadequate clinical response to at least one disease-modifying anti-rheumatic drug (either synthetic or biologic) and are currently receiving a stable dose of methotrexate. Patients who have previously received one or two biologic treatments in total for rheumatoid arthritis will be allowed to participate in the study. Patients who have previously received more than two biologic treatments for rheumatoid arthritis will not be permitted to participate in the study.

Data from this study combined with the Phase I pharmacokinetic equivalence study MS200740-0001 in healthy volunteers [2] will provide evidence to support similarity between MSB11456 and Actemra/RoActemra in terms of pharmacokinetics, efficacy, safety, tolerability and immunogenicity.

1.4 Clinical Experience

A Phase I study (Study MS200740-0001) has been conducted by the Sponsor to compare the pharmacokinetic, pharmacodynamic, safety, tolerability and immunogenicity of a single subcutaneous dose of MSB11456, US-licensed Actemra and EU-approved RoActemra in healthy subjects [2]. The aim of this study was to demonstrate pharmacokinetic equivalence and to compare the pharmacodynamic profiles of the subcutaneous formulation of the proposed biosimilar to tocilizumab (MSB11456, 162 mg/0.9 mL) and the subcutaneous formulation of both the US-licensed reference product (Actemra®, 162 mg/0.9 mL) and the EU-approved reference medicinal product (RoActemra, 162 mg/0.9 mL).

MSB11456 has previously undergone extensive analytical characterization compared to the reference product Actemra and the reference medicinal product RoActemra. The pharmacokinetic equivalence between MSB11456, US-licensed Actemra and EU-approved RoActemra was demonstrated in the Phase I study MS200740-0001 [2]. Safety, tolerability and immunogenicity profiles were also similar between subjects receiving MSB11456 and US-licensed Actemra or EU-approved RoActemra. In this study, the 90% confidence intervals of the geometric least square mean ratios (MSB11456/US-licensed Actemra, MSB11456/EU-approved RoActemra and US-licensed Actemra/EU-approved RoActemra) for the $AUC_{0\text{-last}}$ (area under the plasma drug concentration-time curve up to the last quantifiable time point), $AUC_{0\text{-inf}}$ (area under the concentration-time curve from time 0 extrapolated to infinity) and C_{max} (maximum plasma concentration) were all entirely contained within the predefined equivalence interval of 80% to 125%. Therefore, MSB11456 showed an equivalent pharmacokinetic profile to the two reference treatments, US-licensed Actemra and EU-approved RoActemra and US-licensed Actemra showed an equivalent pharmacokinetic profile to EU-approved RoActemra, following a single subcutaneous injection administration of 162 mg.

Please refer to the European Product Information (RoActemra® Summary of Product Characteristics) [1] and the latest edition of the MSB11456 Investigator's Brochure [2] for a detailed description of the pharmacokinetic, pharmacodynamic and safety profile of tocilizumab.

2 STUDY OBJECTIVES

2.1 Primary

The primary objective of the study is to demonstrate equivalent efficacy of proposed biosimilar tocilizumab MSB11456 and EU-approved RoActemra both administered subcutaneously to patients with moderately to severely active rheumatoid arthritis.

2.2 Secondary

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

2.3 Exploratory

- To explore the effects of a single treatment transition (i.e., in patients who transitioned from EU-approved RoActemra to MSB11456) on efficacy, safety and immunogenicity.

- To describe pharmacokinetic parameters of MSB11456 and RoActemra.

3 STUDY ENDPOINTS

3.1 Primary

The primary efficacy endpoint is the mean absolute change from baseline in Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR) at Week 24.

3.2 Secondary

Secondary endpoints are as follows:

Efficacy:

- DAS28-ESR mean absolute change from baseline at all assessment visits (except Week 1) (i.e., at Weeks 2, 4, 8, 12, 16, 30, 42 and 52) other than Week 24.
- ACR20 (20% improvement in ACR Core Set Measurements) response rate at Week 24.

Safety:

- Occurrence of treatment-emergent adverse events up to Week 24, Week 30, Week 55 and Week 63.
- Occurrence of serious adverse events up to Week 24, Week 30, Week 55 and Week 63.

Immunogenicity:

- Antidrug antibody incidence at Weeks 2, 12, 24, 30, 52 and 55.
- Antidrug antibody titer at Weeks 2, 12, 24, 30, 52 and 55.
- Neutralizing antibody incidence at Weeks 2, 12, 24, 30, 52 and 55.

3.3 Other

Efficacy:

- Disease Activity Score 28-C-Reactive Protein (DAS28-CRP) mean change from baseline at all assessment visits (except Week 1) (i.e., at Weeks 2, 4, 8, 12, 16, 24, 30, 42 and 52).
- ACR20 response rates at all assessment visits (except Week 1) other than Week 24.

- ACR50/70 (50% and 70% improvement in ACR Core Set Measurements) response rates at all assessment visits (except Week 1).

- Proportion of patients with DAS28-ESR and DAS28-CRP categorical responses (remission, Low Disease Activity and ACR/European League Against Rheumatism (EULAR) criteria (Boolean-based) responses categories) at all assessment visits (except Week 1).

- Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) changes from baseline and categories (i.e., remission and Low Disease Activity) at all assessment visits (except Week 1).

Safety:

- Changes in vital signs, clinical laboratory values (hematology, clinical chemistry, urinalysis), abnormalities in 12-lead electrocardiogram and physical examination up to Week 24, Week 30, Week 55 and Week 63.

3.4 Exploratory

Pharmacokinetic exploratory endpoints are:

- Trough concentration.

- Model-based pharmacokinetic parameters (including, but not limited to, predicted C_{max} and area under the concentration-time curve) using a population pharmacokinetic model.

4 STUDY PLAN

4.1 Study Design

This is a multicenter, randomized (1:1), active-controlled, double-blind, multiple fixed-dose, multinational, two-arm, parallel-group study to compare the efficacy, safety and immunogenicity of the proposed biosimilar candidate MSB11456 versus EU-approved RoActemra in patients with moderately to severely active rheumatoid arthritis. In a separate sub-study, the population pharmacokinetic of MSB11456 and EU-approved RoActemra will be described.

This study will enroll patients with moderately to severely active rheumatoid arthritis who have an inadequate response to ≥1 disease-modifying anti-rheumatic drug(s) which may include biologic disease-modifying anti-rheumatic drugs and who are currently receiving a stable dose of methotrexate (refer to eligibility criteria in Section 5.2 and Section 5.3). Patients who have previously received one or two biologic treatments in total for rheumatoid arthritis may be allowed to participate in the study. However, the population of patients with previous exposure to any biologic treatment will be capped at 10% of the total study population. Patients who have previously received more than two biologic treatments for rheumatoid arthritis will not be permitted to participate in the study.

Patients must have received methotrexate for at least 12 consecutive weeks immediately prior to randomization and are on a stable dose between 10 and 25 mg/week methotrexate for the last 8 weeks prior to screening. Patients will continue to take the same stable dose of methotrexate during the 52-week treatment period of the study. All other disease-modifying anti-rheumatic drugs must be withdrawn prior to randomization.

The study will have a duration of up to 67 weeks and will include a Screening Period of a maximum of 28 days prior to first study drug administration, a double-blind 24-week Core Treatment Period (Day 1 to Day 169/Week 24), an additional 28-week double-blind Extended Treatment Period (Day 169/Week 24 to Day 365/Week 52) and a 12-week Safety Evaluation Period. A Safety Follow-Up Visit will be performed at Week 55, 4 weeks after the last dose of study drug at Week 51 and a final End of Study Visit will be conducted at Week 63, 12 weeks after the last dose of study drug at Week 51. (Note: The 12-week Safety Evaluation starts at Week 51, after the last study drug injection and the Extended Treatment Period ends at Week 52.) The end of the study for each patient is defined as the patient's last visit.

Patients whose eligibility is confirmed at baseline will be randomized in a 1:1 ratio by an Interactive Response Technology (IRT) system to receive either MSB11456 or the EU-approved RoActemra at a dose of 162 mg delivered by subcutaneous injection

starting at Day 1, then weekly up to Week 51 inclusive. Randomization will be stratified by previous exposure to biologic treatment for rheumatoid arthritis (yes/no).

The first three doses of study drug (162 mg at Day 1, Day 8 and Day 15) will be administered on-site to ensure the patient or their caregiver is appropriately trained. Patients will be monitored for 2 hours following these first three doses of study drug. The following weekly doses of study drug can be self-administered if the patient is able to self-administer him/herself at the discretion of the Investigator. Patients will check their axillary temperature prior to the self-administration of study drug. In the case of an elevated temperature, it is the Investigator's decision to determine any further actions according to local practice and their medical judgment.

The primary efficacy endpoints will be evaluated at Week 24 (7 days after the 24th study drug administration), along with other endpoints. At Week 24, after all efficacy and safety assessments have been performed, patients will enter the Extended Treatment Period. Patients who were originally randomized to receive RoActemra will be re-randomized in a 1:1 ratio to continue their weekly treatment with RoActemra or to switch to MSB11456 starting at Week 24. Patients who discontinue the study before Week 24 will not be re-randomized. Patients who were originally randomized to MSB11456 will continue this treatment for the complete 52 weeks of study treatment. During the Extended Treatment Period, efficacy, safety and immunogenicity data will be analyzed up to Week 52 with the last assessment performed 7 days after the last study drug administration (i.e., on Week 51).

Safety data will be collected and analyzed at Weeks 55 and 63 (i.e., 4 and 12 weeks after the last study drug administration, respectively). Samples for immunogenicity analysis will be collected at Week 55.

In order to minimize missing data in the evaluation of the treatment effect under the treatment policy strategy, patients who discontinue treatment early or violate the protocol should continue to be followed for all regularly scheduled visits for safety and efficacy assessments up to the end of the corresponding treatment period.

Efficacy, safety and immunogenicity assessments are detailed in the Schedule of Assessments (Table 1). Pharmacokinetic trough concentration samples will be collected from all study patients at scheduled visits.

Patients may be asked to participate in a population pharmacokinetic sub-study performed during the 24-week Core Treatment Period (Day 1 to Day 169/Week 24) and contribute additional pharmacokinetic samples. Participation in the population pharmacokinetic sub-study is optional. Eight additional post-dose pharmacokinetic samples will be collected in each of the patients included in a pharmacokinetic subset of up to approximately 60 patients (approximately 30 from both arms) to enable a

population pharmacokinetic model of tocilizumab concentration-time course in rheumatoid arthritis patients.

4.2 Study Duration

The study will have a duration of up to 67 weeks per patient and will include a Screening Period of maximum 28 days prior to first study drug administration, 24-week Core Treatment Period (Day 1 to Day 169/Week 24) and a 28-week Extended Treatment Period (Day 169/Week 24 to Day 365/Week 52). A Safety Follow-Up Visit will be performed at Week 55, 4 weeks after the last dose of study drug at Week 51 and a final End of Study Visit will be conducted at Week 63, 12 weeks after the last dose of study drug at Week 51. (Note: The 12-week Safety Evaluation starts at Week 51 after the last study drug injection and the Extended Treatment Period ends at Week 52.)

The end of the study will be the date when the last patient has completed the last study assessment.

4.3 Discussion of Study Design

4.3.1 Scientific Rationale for Study Design

The main elements of the study including the study population, route of administration, dosing regimen, primary and secondary efficacy endpoints and their acceptance ranges, as well as the primary analysis population was discussed with regulatory agencies.

The primary objective of this study is to demonstrate equivalent efficacy of the proposed biosimilar MSB11456 and EU-approved RoActemra both administered subcutaneously based on DAS28-ESR at Week 24 in patients with moderately to severely active rheumatoid arthritis.

The timing of the primary efficacy analysis at Week 24 is based on the availability of historical data from the originator's tocilizumab Phase III clinical studies at this time point, on which the assumptions for the equivalence margin and sample size are based.

This study incorporates a transition design. If a patient discontinues study drug prior to Week 24, the patient will remain in the study up to the completion of the Week 24 assessments to allow for the collection of efficacy, safety and immunogenicity data for the assessment of similarity for a full 24-week period before switching occurs. At the Week 24 Visit patients on the RoActemra treatment will be re-randomized and all patients still treated at Week 24 in each arm will enter a further 28-week Extended Treatment Period (Day 169/Week 24 to Day 365/Week 52). The transition design is incorporated into the study in order to collect comparative efficacy and safety data after switching a proportion of patients from the EU-approved RoActemra to the proposed

biosimilar MSB11456 at Week 24. In addition, the 28-week Extended Treatment Period will allow for the collection of safety, immunogenicity and efficacy data for MSB11456 versus EU-approved RoActemra for up to 1 year of treatment. If a patient discontinues study drug during the Extended Treatment Period, the patient will be followed-up until the End of Study Visit. They are NOT considered withdrawn from the study. Patients that discontinue study drug prematurely should be followed for at least 4 weeks after the last study drug dose and either complete a 4-week Safety Follow-Up Visit or have the corresponding assessments completed at a suitable scheduled visit.

This study will enroll patients with moderately to severely active rheumatoid arthritis who have an inadequate response to at least one disease-modifying anti-rheumatic drug (either synthetic or biologic) and who are currently receiving a stable dose of methotrexate. In order to have as homogenous population as possible, only patients who have previously received as a maximum one or two biologic treatments in total for rheumatoid arthritis will be allowed to participate in the study. Patients who have previously received more than two biologic treatments for rheumatoid arthritis will not be permitted to participate in the study. Note: The population of patients with previous exposure to any biologic treatment will be capped at 10% of the total study population.

Since previous exposure to biological treatment is a known factor affecting efficacy, patients will be stratified by previous exposure to biological treatment for rheumatoid arthritis (yes/no) (Burmester, 2014 [3], Kivitz, 2014 [4]). The randomization at Day 1 and Week 24 will use the same stratification factors. Body weight is also known to have an impact on efficacy, namely higher than 100 kg would result in lower treatment effect. This factor is managed at population level with inclusion criterion 2 (Burmester, 2014 [3], Kivitz, 2014 [4]).

This study requires all patients to take a stable dose between 10 and 25 mg/week methotrexate for the last 8 weeks prior to screening. The route of methotrexate administration must also be constant for the study duration. As stable disease severity on methotrexate medication prior to initiating treatment with the study drug is required, the patient must have been taking methotrexate for at least the time required for the clinical effect to be established and at a clinically optimal dose (i.e., for at least 12 weeks prior to randomization). Patients will continue to take the same stable dose of methotrexate during the 52-week treatment period of the study.

The clearance of tocilizumab is concentration-dependent with non-linear (target-mediated) and linear (non-target-mediated) components. Most of the clearance and therefore area under concentration curve after subcutaneous dosing of 162 mg is due to the non-linear (target-mediated) pathway (Abdallah, 2017 [5]). In order to compare (among other processes) the target-mediated clearance of the study drugs, a subset of patients will be asked to consent to participate in a population pharmacokinetic sub-study (EMA/CHMP/BMWP/403543/2010 [6]).

4.3.2 Rationale for Efficacy Endpoints

Efficacy assessments will be performed according to the EULAR/ACR recommendations for reporting disease activity in clinical studies of patients with rheumatoid arthritis. These include validated composite endpoints as measures of clinical response (ACR20/50/70) as well as disease state (Disease Activity Score-28 Joint Count (DAS28), SDAI and CDAI) (Aletaha, 2008 [7]).

The DAS28, CDAI and SDAI are three out of the six rheumatoid arthritis disease activity measures recommended and endorsed by the ACR to facilitate clinical decision making in practice and are based on accurate reflections of disease activity, sensitivity to change, good discrimination between low, moderate, and high disease activity states, incorporation of remission criteria and feasibility to perform in clinical settings (Anderson, 2012 [8]).

The DAS28 (Prevoo, 1995 [9]) is a continuous composite endpoint with differential weighting given to each of the following components:

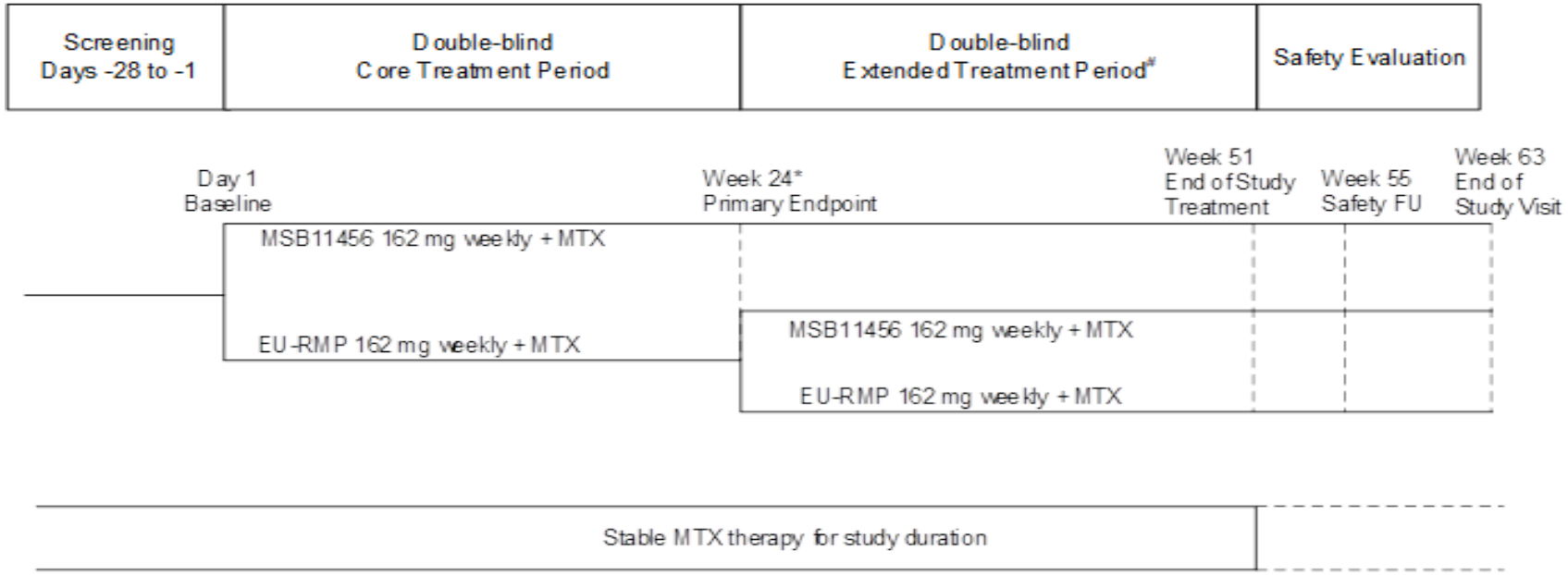
- Tender Joint Count (28 joints).
- Swollen Joint Count (28 joints).
- Patient's Global Assessment of Disease Activity.
- Acute Phase Reactant (C-reactive protein or erythrocyte sedimentation rate).

The DAS28 is a sensitive and specific tool to measure disease activity in rheumatoid arthritis. Continuous indices such as the DAS28 combine both a measure of improvement (i.e., good, moderate or no response to therapy [the EULAR response criteria]) with reaching a specific disease activity state (i.e., remission, low, moderate or high). In this study both DAS28-ESR and DAS28-CRP will be used.

All components of the SDAI are variables of the EULAR and ACR Core Set of variables: Tender Joint Count (28 joints), Swollen Joint Count (28 joints), Physician's Global Assessment of Disease Activity, Patient's Global Assessment of Disease Activity and acute phase reactant (C-reactive protein) (Smolen, 2003 [10]). The CDAI does not include the acute phase reactant variable. Cut-off points to differentiate disease activity states on the SDAI and CDAI scales have been defined, with remission cut-off points for SDAI and CDAI of $\leq$3.3 and $\leq$2.8 respectively (Aletaha, 2005 [11]). The measurement of the efficacy endpoints at each regular visit will allow assessment of the course of the treatment effect during the full year treatment duration.

The ACR response rate is a widely used measure for assessing improvement in rheumatoid arthritis in clinical studies. It is a dichotomous composite endpoint indicating the proportion of patients with at least 20 (50/70) % improvement from baseline in the number of tender and swollen joints and in three or more out of the five ACR Core Set measures: Patient's Assessment of Arthritis Pain (Visual Analog Scale), physical function assessment (Health Assessment Questionnaire-Disability Index), acute phase reactant concentration (C-reactive protein or erythrocyte sedimentation rate), Patient's Global Assessment of Disease Activity (Visual Analog Scale) and Physician's Global Assessment of Disease Activity (Visual Analog Scale).

4.4 Study Schematic



*At the Week 24 Visit, patients remaining on-study treatment who had received MSB11456 during the Core Treatment Period will continue to receive MSB11456 during the Extended Treatment Period. Patients who had received EU-approved RoActemra® during the Core Treatment Period will be randomized 1:1 to receive either MSB11456 or EU-approved RoActemra® during the Extended Treatment Period. The Week 24 primary efficacy analysis will be conducted after all patients have completed the Week 30 assessments, or have terminated the study before Week 30. An independent team will perform the analysis at Week 24.
#The 12-week Safety Evaluation starts at Week 51 and the Extended Treatment Period ends at Week 52. The investigators and patients will remain blinded to treatment allocations during the double blind Extended Treatment Period. However, the Sponsor will be unblinded at the time of the Week 30 analysis.

Abbreviations: EU-RMP=European Union-Approved Reference Medicinal Product=RoActemra®; FU=Follow-Up; MTX=methotrexate

4.5 Schedule of Assessments

Table 1 Schedule of Assessments – Main Study

Trial Period	**Screening**	**Core Treatment Period**								**Extended Treatment Period**			**Early Termination**	**Safety Follow-Up**	**End of Study Visit**
Visit number and week	**1**	**2** **Base-line**	**3** **W1**	**4** **W2**	**5** **W4**	**6** **W8**	**7** **W12**	**8** **W16**	**9** **W24[y]**	**10** **W30[z]**	**11** **W42**	**12** **W52 (EOT + 1 wk)**	**ET[x]**	**13** **W55** **(4 weeks after the last study drug dose)**	**14** **W63** **(12 weeks after the last study drug dose – Safety Evaluation Period)**
Visit Day/Window (days)	**-28 to -1 days (n.a.)**	**D1 (None)**	**D8 (±2)**	**D15 (±2)**	**D29 (±2)**	**D57 (±2)**	**D85 (±2)**	**D113 (±2)**	**D169 (±2)**	**D211 (±2)**	**D295 (±4)**	**D365 (±4)**		**D386 (±7)**	**D442 (± 7)**
Informed consent[a]	X														
Disease Assessments															
Efficacy assessments[b]	X	X		X	X	X	X	X	X	X	X	X	X		
Clinical Assessments															
Medical history[c]	X	X[d]													
Demographics	X														
Inclusion/exclusion criteria	X	X[e]													
Physical examination	X[f]	X[g]			X[g]		X[g]		X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram	X								X			X	X[i]	X[i]	X
Chest X-ray[j]	X												X[k]		X[k]

Trial Period	**Screening**	**Core Treatment Period**								**Extended Treatment Period**			**Early Termination**	**Safety Follow-Up**	**End of Study Visit**
Visit number and week	**1**	**2** **Base-line**	**3** **W1**	**4** **W2**	**5** **W4**	**6** **W8**	**7** **W12**	**8** **W16**	**9** **W24[y]**	**10** **W30[z]**	**11** **W42**	**12** **W52 (EOT + 1 wk)**	**ET[x]**	**13** **W55** **(4 weeks after the last study drug dose)**	**14** **W63** **(12 weeks after the last study drug dose – Safety Evaluation Period)**
Visit Day/Window (days)	**-28 to -1 days (n.a.)**	**D1 (None)**	**D8 (±2)**	**D15 (±2)**	**D29 (±2)**	**D57 (±2)**	**D85 (±2)**	**D113 (±2)**	**D169 (±2)**	**D211 (±2)**	**D295 (±4)**	**D365 (±4)**		**D386 (±7)**	**D442 (± 7)**
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection site reactions[m]		X	X	X	X	X	X	X	X	X	X	X	X		
Collection and review of patient diary[n]					X	X	X	X	X	X	X	X	X		
Pharmacokinetic Sampling															
Pharmacokinetic trough concentration sampling[o]		X	X	X	X	X	X		X	X	X	X	X		
Laboratory Assessments															
Clinical chemistry[p], hematology, coagulation and lipid panel	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X		X	X		X		X	X		X	X	X	X
Erythrocyte sedimentation rate (as part of DAS28-ESR assessment)[b]	X	X		X	X	X	X	X	X	X	X	X	X		

[redacted]

Trial Period	**Screening**	**Core Treatment Period**								**Extended Treatment Period**			**Early Termination**	**Safety Follow-Up**	**End of Study Visit**
Visit number and week	**1**	**2** **Base-line**	**3** **W1**	**4** **W2**	**5** **W4**	**6** **W8**	**7** **W12**	**8** **W16**	**9** **W24[y]**	**10** **W30[z]**	**11** **W42**	**12** **W52 (EOT + 1 wk)**	**ET[x]**	**13** **W55** **(4 weeks after the last study drug dose)**	**14** **W63** **(12 weeks after the last study drug dose – Safety Evaluation Period)**
Visit Day/Window (days)	**-28 to -1 days (n.a.)**	**D1 (None)**	**D8 (±2)**	**D15 (±2)**	**D29 (±2)**	**D57 (±2)**	**D85 (±2)**	**D113 (±2)**	**D169 (±2)**	**D211 (±2)**	**D295 (±4)**	**D365 (±4)**		**D386 (±7)**	**D442 (± 7)**
C-reactive protein (as part of the SDAI Score and DAS28-CRP)[b]	X	X		X	X	X	X	X	X	X	X	X	X		
Follicle-stimulating hormone test (women only)	X														
Serum pregnancy test	X														
Urine pregnancy test[q]		X			X	X	X	X	X	X	X	X	X	X	
Viral serology[r]	X												X		X
Anti-nuclear antibodies, anti-double-stranded DNA, rheumatoid factor, anti-cyclic citrullinated peptide antibodies	X						X					X	X	X	
QuantiFERON®-TB Gold Plus test[s]	X								X			X	X	X	
Immunogenicity sampling[t]	X[u]	X		X			X		X	X		X	X	X	
Treatments Administered															
Randomization		X							X[v]						

Trial Period	**Screening**	**Core Treatment Period**								**Extended Treatment Period**			**Early Termination**	**Safety Follow-Up**	**End of Study Visit**
Visit number and week	**1**	**2** **Base-line**	**3** **W1**	**4** **W2**	**5** **W4**	**6** **W8**	**7** **W12**	**8** **W16**	**9** **W24[y]**	**10** **W30[z]**	**11** **W42**	**12** **W52 (EOT + 1 wk)**	**ET[x]**	**13** **W55** **(4 weeks after the last study drug dose)**	**14** **W63** **(12 weeks after the last study drug dose – Safety Evaluation Period)**
Visit Day/Window (days)	**-28 to -1 days (n.a.)**	**D1 (None)**	**D8 (±2)**	**D15 (±2)**	**D29 (±2)**	**D57 (±2)**	**D85 (±2)**	**D113 (±2)**	**D169 (±2)**	**D211 (±2)**	**D295 (±4)**	**D365 (±4)**		**D386 (±7)**	**D442 (± 7)**
Trial medication administered[w]		X	X	X	X	X	X	X	X	X	X				

D=day; DAS28-CRP=Disease Activity Score-28 C-Reactive Protein; Disease Activity Score-28 Erythrocyte Sedimentation Rate; EOT=End of Treatment; ET=Early Termination; n.a.=not applicable; SDAI=Simplified Disease Activity Index; W/wk=week

a. Informed consent must be obtained from each patient prior to performing any screening assessments. Note: A separate Informed Consent Form (containing important information about COVID-19, clinical research study participation and patient consent) will be provided to and signed by each patient to provide information on the general risks of study participation related to COVID-19 and to document that it is understood by the patient. Another separate Informed Consent Form will be required to be understood and signed by partners of male participating patients who become pregnant during the study or within 10 weeks after the participating patient's last dose of study drug.
b. Efficacy assessments: Tender Joint Count, Swollen Joint Count, erythrocyte sedimentation rate, C-reactive protein, Health Assessment Questionnaire-Disability Index, Patient Assessment of Arthritis Pain, Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity. Patient-reported outcome questionnaires should be the first assessments performed after the temperature measurements at the visits for which they are scheduled. Note: only Tender Joint Count and Swollen Joint Count assessments will be performed at screening (to confirm inclusion criterion 4 for at least six tender and swollen joints) and will be confirmed again at baseline. After confirmation at baseline, Tender Joint Count and Swollen Joint Count assessments will be performed at the scheduled timepoints. All other efficacy assessments will be performed only at baseline (once the patient has qualified) and then at the scheduled timepoints.
c. Medical history must include rheumatoid arthritis disease phenotype and duration as well as date of first diagnosis, previous treatments including any previous biologic or non-biologic therapy for rheumatoid arthritis, history of tuberculosis or any treatment for active/latent tuberculosis, previous surgeries and smoking status.
d. Review and update medical history only, to ensure the patient remains qualified for the study.
e. Re-check screening results (including virus serology and tuberculosis test) to ensure the patient remains eligible to participate in the study.
f. A complete physical examination including height and body mass index is performed at screening. Weight will be measured at screening and baseline.
g. Only physical examination and weight are performed at the indicated visits.

h. Vital signs (including body temperature, respiratory rate, heart rate [after a 5 minute rest] and arterial blood pressure [after a 5 minute rest]) will be measured using a validated device and will be recorded at the Screening Visit and throughout the study at the visits indicated in the Schedule of Assessments. During the study, measurement of vital signs may be repeated at the discretion of the Investigator for safety reasons. Axillary body temperature measurement should be performed first at each study visit and should precede every other assessment of each visit. In the case of an elevated temperature, it is the Investigator's decision to determine any further actions according to local practice and their medical judgment.
i. The electrocardiogram will be repeated at the Safety Follow-Up Visit at Week 55 only if in the opinion of the Investigator it is clinically warranted (e.g., supported by corresponding signs and symptoms).
j. If a bidirectional chest X-ray is available within the 3 months before randomization, the X-ray will not be required to be repeated at screening.
k. Only if the QuantiFERON®-TB Gold Plus test is positive at the Early Termination Visit or the End of Study Visit. If the QuantiFERON®-TB Gold Plus test is indeterminate, patients may be retested once. If on retest the result is positive or indeterminate then the patient must undergo a chest X-ray.
l. Confirmed COVID-19 cases should be considered by the Investigator as 'otherwise medically important' and accordingly reported as serious adverse events.
m. In addition to the inspection of the injection site, the Investigator is also requested to ask the patient during the assessment about any such reactions that may have occurred since last assessment (see Section 7.13).
n. Patients will receive their Patient Diaries on Visit 4.
o. Pharmacokinetic trough concentration will be collected from all patients in conjunction with the immunogenicity sampling (except at Week 1 when only trough concentration sample is drawn). These samples must be collected prior to the immunogenicity sampling and prior to the study drug administration.
p. Additional unscheduled serum chemistry samples can be collected from those patients who receive anti-fungal drugs or any other medication with known liver toxicity during the study treatment phase.
q. Urine pregnancy tests will be performed for women of childbearing potential at baseline before dosing with study drug and pre-dose at Weeks 4, 8, 12, 16, 24, 28, 32, 42 and 52, Early Termination and Follow-Up Visit at Week 55. When there is no site visit, the patients will perform the urine pregnancy tests at home every 4 weeks.
r. Includes tests for human immunodeficiency virus subtype 1 (HIV-1) and subtype 2 (HIV-2), hepatitis B virus surface antigen, hepatitis B virus core antibody and hepatitis C virus antibody. Note: Reflex testing for hepatitis C virus RNA and hepatitis B virus DNA is allowed if hepatitis C virus antibodies or hepatitis B virus antibodies are present without a positive result for hepatitis B virus surface antigen.
s. Continuation of study medication will be excluded in patients who were QuantiFERON®-TB Gold Plus test negative at randomization, but subsequently become QuantiFERON®-TB Gold Plus positive at Week 24. Patients whose QuantiFERON®-TB Gold Plus test is indeterminate at Week 24 may be retested once. If on retest the result is positive or indeterminate then the patient must be withdrawn from the study. The QuantiFERON®-TB Gold Plus test need not be repeated if the patient has had a QuantiFERON®-TB Gold Plus test performed within 4 weeks before the Early Termination Visit.
t. Blood samples for immunogenicity assessments must be drawn prior to the administration of the study drug, which will be performed at the site for these visits. Separate samples will be collected for antidrug antibody and neutralizing antidrug antibody assessments. In order to evaluate antidrug antibodies in all patients who discontinue from the study at Week 24 (or any subsequent visit), a blood sample for immunogenicity assessment must be taken 4 weeks after last dose of study drug.
u. No result will be reported; sample will only be used for method validation purposes and establishment of assay cut-off points for immunogenicity analysis. These are required to statistically determine positive from negative samples.
v. Re-randomization of patients (initially randomized to EU-approved RoActemra) to continue with RoActemra or being switched to MSB11456.
w. On weeks with scheduled study visits, the study drug will be administered by the site staff. On weeks with no scheduled study visit, the patient (or caregiver) will inject the study drug. Patients will be monitored for 2 hours following the first, second and third doses of study drug at baseline (Day 1), and Weeks 1 and 2. The last dose of study drug will be administered at Week 51 at home.
x. Any patient who prematurely withdraws or is withdrawn from the study must complete the Early Termination procedures. If a patient discontinues study drug prior to Week 24, the patient will remain in the study up to the completion of the Week 24 assessments to allow for the collection of efficacy, safety and immunogenicity data for the assessment of similarity for a full 24-week period before switching occurs. If a patient discontinues study drug during the Extended Treatment Period, the patient will

be followed-up until the End of Study Visit. They are NOT considered withdrawn from the study. Patients that discontinue study drug prematurely should be followed for at least 4 weeks after the last study drug dose and either complete a 4-week Safety Follow-Up Visit or have the corresponding assessments completed at a suitable scheduled visit.

y. All patients will remain in the study up to the completion of the Week 24 assessments to allow for the collection of efficacy, safety and immunogenicity data for the assessment of biosimilarity for a full 24-week period before switching occurs. After the Week 24 Visit patients will be re-randomized and enter a further 28-week Extended Treatment Period (Day 169/Week 24 to Day 365/Week 52).

z. Week 30 is the first clinic visit of the Extended Treatment Period after the Week 24 Visit.

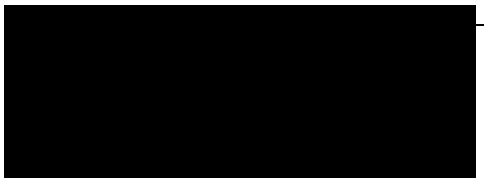


Table 2 Schedule of Assessments – Population Pharmacokinetic Sub-Study

Visit Day	**Day 1**	**Day 1**	**Day 5**	**Day 9**	**Day 13**	**Day 14**	**Day 16**	**Day 24**
Time relative to previous dose in days (hours)	0.5 (12 hours ±2 hours)	1 (24 hours ±2 hours)	4 (96 hours ±6 hours)	1.5 (36 hours ±2 hours)	5 (120 hours ±4 hours)	6 (144 hours ±4 hours)	1 (24 hours ±2 hours)	2 (48 hours ±24 hours)
Pharmacokinetics	X	X	X	X	X	X	X	X

In addition to the trough samples collected from all patients shown in Table 1, samples specific for the pharmacokinetic sub-study analyses will be collected at the time points shown in this table. Note: The time relative to the previous dose and visit window presented in this table supersede those of Table 1 if the patient is included in the sub-study.

5 POPULATION

5.1 Number of Patients

A sample size of 542 randomized patients (271 patients per treatment group) is chosen to provide approximately 460 patients (230 patients per treatment) in the Per Protocol Analysis Set at Week 24, assuming a 15% drop-out rate (including major protocol deviations). It is planned to have approximately 100 study centers in approximately 10 countries (Europe).

5.2 Inclusion Criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled by male and female patients with moderately to severely active rheumatoid arthritis who:

1. Are ≥18 years of age.

2. Have a body weight of <100 kg at screening.

3. Diagnosis of rheumatoid arthritis according to the revised 1987 ACR/EULAR Classification 2010 criteria with disease duration of ≥6 months prior to the Screening Visit.

4. Have moderately to severely active rheumatoid arthritis as defined by:

    a. Swollen Joint Count ≥6 (66 joint count) and Tender Joint Count ≥6 (68 joint count) at screening and randomization.

    b. Radiographic evidence of ≥1 joint with a definite erosion attributable to rheumatoid arthritis at screening. The radiographic evidence of joint erosion should be no older than 6 months.

    c. C-reactive protein ≥1 mg/dL (≥10 mg/L) and/or erythrocyte sedimentation rate ≥28 mm/hour at screening.

5. Must have been treated with methotrexate for at least 12 consecutive weeks immediately prior to randomization and are on a stable dose between 10 and 25 mg/week methotrexate for the last 8 weeks prior to screening. Note: Oral and/or subcutaneous administration of methotrexate is allowed.

6. Must be willing to receive at least 5 mg/week or equivalent of folic acid.

7. Have had previous inadequate clinical response to at least one modifying anti-rheumatic drug (either synthetic or biologic).

8. Have withdrawn all disease-modifying anti-rheumatic drugs other than methotrexate at least 8 weeks prior to randomization with the exception of leflunomide which must have been discontinued for ≥12 weeks prior to randomization (or ≥4 weeks after 11 days of standard cholestyramine washout).

9. Had discontinued biologic treatment for ≥12 weeks prior to randomization. Note: The population of patients with previous exposure to any biologic treatment will be capped at 10% of the total study population.

10. Must be able and willing to self-administer subcutaneous injections or have a qualified/trained person(s) available to administer subcutaneous injections.

11. Women of childbearing potential (i.e., considered fertile following menarche and until becoming postmenopausal unless permanently sterile) can participate only if they have a negative serum pregnancy test at screening and a negative urine pregnancy test at Day -1 before randomization. Women of childbearing potential must have used and agree to use a highly effective contraception (i.e., methods with a failure rate of less than 1% per year) as detailed in Appendix III, for 4 weeks before randomization and must agree to continue to practice adequate contraception for 3 months after the last study drug administration (see Appendix III).

    Women of childbearing potential whose preferred lifestyle is total abstinence from intercourse may participate in the study.

    Withdrawal and rhythm methods are not considered to be highly effective methods of contraception and are not permitted as the sole method of contraception in this study.

12. Women who are postmenopausal (i.e., age-related amenorrhea ≥12 consecutive months and increased follicle-stimulating hormone >40 mIU/mL), or women who have undergone documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy are exempt from pregnancy testing (see Appendix III). If necessary to confirm postmenopausal status, a follicle-stimulating hormone sample will be tested at screening.

    Females on hormone replacement therapy and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their hormone replacement therapy during the study. Otherwise, they must discontinue hormone replacement therapy to allow confirmation of postmenopausal status before study enrollment. Women who were taking hormone replacement therapy prior to study entry are allowed to participate in the study if they

have a negative pregnancy test at screening and prior to randomization. Initiating hormone replacement therapy during the study is not permitted.

13. Men must either be surgically sterile (vasectomy with documented confirmation of aspermia) or must agree to use a condom (with spermicide) and to have their female partners agree to use a highly effective contraception (i.e., methods with a failure rate of less than 1% per year as detailed in Appendix III), unless their partners are infertile or surgically sterile, from the time of the first administration of study drug and for at least 3 months after the study drug administration and refrain from donating sperm during this period.

14. Must voluntarily give written informed consent before any study-related activities are performed. Patients must read and fully understand the Informed Consent Form and the requirements of the study. Patients must be willing to comply with all study visits and assessments. Patients must be willing to complete each study procedure. Note: A separate Informed Consent Form (containing important information about COVID-19, clinical research study participation and patient consent) will be provided to and signed by each patient to provide information on the general risks of study participation related to COVID-19 and to document that it is understood by the patient. Another separate Informed Consent Form will be required to be understood and signed by partners of male participating patients who become pregnant during the study or within 10 weeks after the participating patient's last dose of study drug.

5.3 Exclusion Criteria

Patients will be excluded from the study if any of the following criteria are met:

1. American College of Rheumatology functional class IV as defined by the ACR classification of functional status or wheelchair/bedbound (Appendix IV).

2. Rheumatic autoimmune disease or history of/current inflammatory joint disease other than rheumatoid arthritis or significant systemic involvement secondary to rheumatoid arthritis (e.g., Felty's syndrome, vasculitis, pulmonary fibrosis, gout, Lyme disease, psoriatic arthritis). Sjögren's syndrome secondary to rheumatoid arthritis is allowed.

3. Previously received tocilizumab, an investigational or licensed biosimilar of tocilizumab or any interleukin-6 acting drugs (approved or investigational).

4. Prior use of targeted synthetic disease-modifying anti-rheumatic drugs like janus kinase inhibitors (approved e.g., tofacitinib, baricitinib, upadacitinib or investigational e.g., filgotinib, peficitinib).

5. Prior use of any biological agent for a condition other than rheumatoid arthritis (e.g., ranibizumab, denosumab).

6. Prior use of more than two biologic treatments for rheumatoid arthritis.

7. Prior use of biologic investigational drugs (excluding biosimilars) for the treatment of rheumatoid arthritis.

8. Received any investigational drugs within 12 weeks or five drug half-lives (whichever is longer) prior to screening or planned intake of an investigational drug during the course of this trial including the Follow-Up Period.

9. 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 has previously undergone total lymphoid irradiation.

10. Use of non-steroidal anti-inflammatory drugs not at a stable dose for at least 4 weeks prior to randomization or exceeding the maximum recommended dose. Note: Patients are permitted to take aspirin at a dose of ≤325 mg daily for cardiac prophylaxis. Use of paracetamol is allowed in the study.

11. Use of oral corticosteroids >10 mg/day prednisone or equivalent if the dose has not been stable for at least 6 weeks prior to randomization.

12. Intra-articular or parenteral corticosteroids within 4 weeks prior to randomization.

13. Use of high potency opioid analgesics (e.g., hydromorphone, oxycodone, fentanyl, or morphine).

14. Has been treated with intravenous gamma globulin or plasmapheresis within 6 months of randomization.

15. Received a live or attenuated vaccine within 4 weeks prior to randomization.

16. History of hypersensitivity or severe allergic reactions to monoclonal antibodies, any components of the study drug formulations, comparable drugs, or latex.

17. Patient is considered by the Investigator, for any reason, to be an unsuitable candidate for the study. Investigator should specifically evaluate the patient's eligibility taking into consideration COVID-19 risk factors and situation.

18. Has a serious and/or unstable and/or poorly controlled medical condition such as but not limited to poorly controlled diabetes, unstable ischemic heart disease, uncontrolled hypertension (systolic ≥160 mmHg and/or diastolic ≥95 mmHg) or other cardiovascular, cerebrovascular, cardiovascular, gastrointestinal disease, hepatic, renal, hematological (including pancytopenia, aplastic anemia, or blood dyscrasia), endocrine, nervous system or pulmonary disease or other relevant medical condition or a history of clinically significant disease or any other condition that, in the opinion of the Investigator, would put the patient at risk by participation in the study.

19. History of diverticulosis requiring antibiotic treatment or any other gastrointestinal condition (e.g., inflammatory bowel disease, mechanic bowel obstruction, hernia) that might predispose the patient to gastrointestinal perforations.

20. Uncontrolled medical conditions (e.g., asthma, psoriasis) for which flares are commonly treated with corticosteroids or systemic corticosteroid treatment for these conditions within the last 12 months prior to randomization.

21. Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery during the study.

22. History of, or current myeloproliferative or lymphoproliferative disease or malignancy. Curatively treated basal or squamous cell carcinoma of the skin is not excluded, unless it occurred within 12 months of randomization. Curatively treated localized in situ carcinoma of the cervix within 5 years of randomization is also not excluded, if there is no evidence of recurrence prior to randomization.

23. Medical evidence of current or history of primary or secondary immunodeficiency as per Investigator's judgment.

24. Pre-existing or recent-onset central or peripheral nervous system demyelinating disorder, such as multiple sclerosis or optic neuritis, or symptoms suggestive of such a disorder as per Investigator' judgment.

25. Confirmed or, based on the signs and symptoms observed at the time of assessment, suspected active COVID-19 infection at the time of screening and/or randomization.

26. Has had any infection as follows:

    a. Herpes zoster or any opportunistic invasive infection (e.g., histoplasmosis, coccidioidomycosis, blastomycosis, pneumocystis, listeriosis, legionellosis, or parasitic infestations) within 6 months of screening.

    b. Frequent (more than three of the same type of infection per year requiring treatment) chronic or recurrent infections (e.g., urinary tract or upper respiratory tract infections).

    c. A positive test for human immunodeficiency virus subtype 1 (HIV-1) or 2 (HIV-2), hepatitis C antibody, hepatitis B surface antigen and/or core antibody for immunoglobulin G and/or immunoglobulin M or total immunoglobulin at screening.

    d. A serious infection defined as requiring hospitalization or treatment with intravenous antibiotics within 8 weeks prior to randomization.

    e. Required treatment with oral antibiotics and/or anti-fungal drugs within 14 days prior to randomization.

27. Medical evidence of active or latent tuberculosis as indicated by a positive QuantiFERON®-TB Gold Plus test, chest X-ray and/or clinical examination or has had active or latent tuberculosis disease at any time in the past.

    Patients will be screened for latent tuberculosis infection by the QuantiFERON®-TB Gold Plus test and by chest X-ray. Note: If a bidirectional chest X-ray is available within the 3 months before randomization, the X-ray will not be required to be repeated at screening. If a patient tests positive for latent tuberculosis infection at screening, the patient will fail screening and will not be eligible for participation in the study. If the QuantiFERON®-TB Gold Plus test is indeterminate, patients may be retested once within the Screening Period:

    a. If the retest is negative, the patient is eligible to further participate in the study.

    b. If the retest is positive, the patient is not eligible to further participate in the study.

    c. If the retest is again indeterminate, the patient is considered as having latent tuberculosis infection and is not eligible to further participate in the study. No further QuantiFERON®-TB Gold Plus testing will be performed.

28. History of clinically significant drug or alcohol abuse within the last year prior to randomization.

29. Laboratory abnormalities (excluding erythrocyte sedimentation and C-reactive protein values) that were considered clinically significant by the Investigator OR any of the following at screening:

    a. Hemoglobin <8 g/dL for women or 8.5 g/dL for men.

    b. White blood cells <3.5 x 10^9/L.

    c. Absolute neutrophil count <2.0 x 10^9/L.

    d. Platelet count <100 x 10^9/L.

    e. Alanine aminotransferase or aspartate aminotransferase >1.5 times the upper limit of normal (ULN).

    f. Creatinine >1.5 mg/dL if the patient is aged <65 years old, or >ULN if the patient is aged ≥65 years old or proteinuria ≥3+ by dipstick.

    g. Creatinine clearance <50 mL/min (Cockcroft-Gault formula).

30. Received a COVID-19 vaccine within 4 weeks prior to randomization, are receiving ongoing COVID-19 vaccination at the time of screening or plan to receive COVID-19 vaccination before the completion of the Week 30 visit of the study. COVID-19 vaccination is considered ongoing if a multidose regimen has been started but has not been completed.

5.4 Patient Enrollment and Registration

To differentiate screened and randomized patients, within Electronic Data Capture/IRT system, the following process must be adhered to:

- Each patient should have a unique patient screening identification number. This will be assigned at the Screening Visit.
- Once the patient's eligibility has been successfully confirmed, the patient will be randomized and assigned a unique randomization number.
- If the patient withdraws the study participation before/after the Baseline Visit, his/her screening or randomization identification number cannot be re used for another patient.

Investigator(s) should keep a record, the patient screening log, of patients who entered screening.

The Investigator(s) will:

- Obtain signed informed consent from the potential patient before any study and/or sub-study specific procedures are performed. Note: A separate Informed Consent Form providing information on the general risks of study participation related to COVID-19 is required to be understood and signed by all patients. Another separate Informed Consent Form will be required to be understood and signed by partners of male participating patients who become pregnant during the study or within 10 weeks after the participating patient's last dose of study drug.

- Determine patient eligibility.

5.5 Screen Failures

Patients who fail to meet the eligibility criteria for the study at either the Screening or Baseline Visit are screen failures and should not under any circumstances be randomized or receive study medication. There can be no exceptions to this rule. Re-screening of a screen failure patient is not allowed.

Where a patient does not meet all the eligibility criteria but is incorrectly started on treatment, the Investigator should inform the Medical Monitor immediately, and a discussion should occur between the Medical Monitor and the Investigator regarding whether to continue or discontinue the patient from treatment. The Medical Monitor must ensure all decisions are appropriately documented.

The reason for screen failure will be collected in the clinical database. The following information, as a minimum, can be collected in the source documentation only for patients who failed screening: informed consent, age, race, ethnicity, adverse events from the date of informed consent until the patient is considered to have failed screening by the Investigator and the Investigator's signature. Inclusion/exclusion criteria will be only documented in source documents.

6 STUDY CONDUCT

6.1 Study Personnel and Organizations

This clinical study will be sponsored by Fresenius Kabi SwissBioSim GmbH.

The Sponsor will enlist the support of Contract Research Organizations (CROs) to execute the study. The Sponsor will supervise all outsourced activities.

The Sponsor's Clinical Safety and Pharmacovigilance Department or its designated representatives will put in place and oversee suitable risk management and mitigation measures, including risk-monitoring activities and processes to ensure the timely reporting of adverse events and serious adverse events to all concerned parties in accordance with the applicable guidelines, laws and regulations.

The clinical sites shall implement risk minimization and the mitigation plan for COVID-19, including precautions such as use of personal protective equipment for patients, site staff and other visitors, site staff health-check and the disinfection of site premises.

6.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the Investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

6.3 Criteria for Premature Discontinuation

All patients that received at least one dose of study drug in either the 24-week Core Treatment Period or the Extended Treatment Period and who are permanently discontinued from study drug before the end of that period should be encouraged to remain in the study and attend all study visits of the period of discontinuation, irrespective of when they received the last study drug dose, with the aim to collect as much safety and efficacy data as possible. If a patient discontinues study drug prior to Week 24 the patient will remain in the study up to the completion of the Week 24 assessments. If a patient discontinues study drug during the Extended Treatment Period, the patient will be followed-up until the End of the Study Visit.

Patients that discontinue study drug prematurely should be followed for at least 4 weeks after the last study drug dose and either complete a 4-week Safety Follow-Up Visit or have the corresponding assessments completed at a suitable scheduled visit.

Patients that permanently discontinue study drug should not receive any prohibited medications (as defined in Section 8.12) until the completion of the 4-week Safety Follow-Up assessments.

Patients may voluntarily withdraw from the study at any time for any reason. They may be considered withdrawn, if they state an intention to withdraw informed consent or become lost to follow-up.

6.3.1 Reason for Treatment Discontinuation

If premature withdrawal from study drug occurs, the Investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study drug. The date and primary reason for stopping study drug should be recorded in the electronic Case Report Form on the End of Treatment page. In addition, the Investigator must contact the IRT system to register the patient's early permanent treatment discontinuation.

Study drug must be discontinued under the following circumstances:

- Adverse events.
    - Adverse events that in the judgment of the Investigator, taking into account the patient's overall status, prevent the patient from continuing treatment.
    - Due to the language in the label of the comparator in this study (tocilizumab/RoActemra), drug should be stopped if a patient develops: serious infections; gastrointestinal perforations; serious complications of diverticulitis; hypersensitivity reactions, including anaphylaxis; demyelinating disorders; active hepatic disease and hepatic impairment. Please refer to your local label for more information.
    - Any laboratory abnormalities that in the judgment of the Investigator, taking into consideration the patient's overall status, prevent the patient from continuing treatment.
    - Potential Hy's Law events.
    - Anaphylactic or other serious allergic reactions.
    - If study drug cannot be resumed due to a toxicity and/or in case of toxicity that unacceptably endangers the safety of the patient (see Section 8.6).
- Lost to Follow-Up.

- Protocol non-compliance (protocol deviations). Any protocol deviation that results in a significant risk to the patient's safety if the treatment is continued.
    - Use of prohibited treatment following discussion with the Medical Monitor.
- Lack of efficacy.
- Pregnancy.
- Death.
- Withdrawal of consent from treatment.
- Principal Investigator's decision.
    - The Investigator should discontinue study drug for a given patient, if on balance, they think that continuation would be detrimental to the patient's well-being.
- Other.
    - QuantiFERON®-TB Gold Plus test negative at randomization, but subsequently become QuantiFERON®-TB Gold Plus test positive at Week 24 (see Section 7.12.7).

Patients who discontinue study drug for any of the reasons listed above will continue to be followed for efficacy and safety assessments. They are NOT considered withdrawn from the study.

Study drug can be re-introduced if the cause of study drug interruption is solved and the re-start of treatment is medically justified and not otherwise prohibited (e.g., treatment with prohibited medication), nevertheless it requires the approval of Medical Monitor.

6.3.2 Reasons for Study Discontinuation

Reasons for removing a patients from the study may include the following:

- Adverse event.
- Lost to Follow-Up.
- Death.
- Withdrawal of consent from the study.
- Other.

6.3.3 Premature Patient Withdrawal

Although a patient is not obliged to give his/her reason(s) for withdrawing permanently from the study, the Investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the patient's rights. If there is a medical reason for withdrawal, the patient will remain under the supervision of the Investigator until satisfactory health has returned or the patient's status is stabilized.

After study discontinuation patients will be asked to return for the Safety Follow-Up Visit (i.e., Week 55 visit) for their own safety about 4 weeks after the last study drug to monitor adverse events, concomitant medication and immunogenicity (blood sampling for serum trough levels and antidrug measurements). Patients that permanently discontinue study drug should not receive any prohibited medications (defined in as defined in Section 8.12) until the completion of the 4-week Safety Follow-Up assessments.

See Schedule of Assessments (Table 1) for the required assessments of these patients after study discontinuation at the Early Termination Visit.

Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

6.3.4 Lost to Follow-Up

For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

6.3.5 Medical Care of Patients After End of Study

After patients leave the study, medical care will be at the discretion of the Investigator following institutional standard of care and the Sponsor will not provide any additional care to patients.

7 DESCRIPTION OF STUDY PROCEDURES

A detailed schedule of study procedures/assessments is provided in Table 1.

The screening procedures will be performed and completed within 28 to 1 days prior to randomization.

Except for the tuberculosis testing as detailed in the inclusion/exclusion criteria, patients with other test results that do not meet the inclusion/exclusion criteria may have testing repeated once only, if the results are thought to represent a laboratory error or a reversible or a clinically insignificant intermittent condition. Testing can only be repeated upon approval of the Medical Monitor and should be done only for justified cases (i.e., when laboratory results are invalid due to technical reasons or if other technical problems with the sample). If inclusion/exclusion criteria are not met based on the results of the repeated tests, the patient should be considered a screen failure and not be enrolled in the study. Repeat tests should be conducted and results available within 28 to 1 days prior to randomization.

7.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care (see Section 14.4).

Participation in the population pharmacokinetic sub-study is optional. All patients participating in the pharmacokinetic sub-study will sign a separate section of the main Informed Consent Form.

A separate Informed Consent Form (containing important information about COVID-19, clinical research study participation and patient consent) will be provided to and signed by each patient to provide information on the general risks of study participation related to COVID-19 and to document that it is understood by the patient.

Partners of participating male patients who become pregnant, with an estimated conception date during the study or within 3 months after the last administration of the study drug will be asked to sign another separate Informed Consent Form.

7.2 Randomization

Only patients that fulfill all the inclusion criteria and none of exclusion criteria can participate in the study (see Section 5.2 and Section 5.3, respectively). After eligibility is confirmed on Day 1, the patient will be randomized in a double-blind manner by a central IRT system in a 1:1 ratio to receive either EU-approved RoActemra or MSB11456.

Patients will be stratified by previous exposure to biological treatment for rheumatoid arthritis (yes/no).

Patients who have previously received one or two biologic treatments in total for rheumatoid arthritis will be capped at 10% of the total study population.

Blinded treatment kits labeled with individual kit numbers will be provided to each study site. Dosing of study drug will be initiated at the site after randomization. At each visit when study medication is administered and dispensed, the study staff will contact the IRT to obtain appropriate kit numbers.

At the end of Week 24 Visit, after all planned assessments have been conducted and the Investigator has confirmed that the study drug does not need to be discontinued (see Section 6.3 for criteria for patient withdrawal), patients will be re-randomized by the IRT system for a further 28 weeks of treatment. The same stratification factor will be used for the randomization and re-randomization. Patients initially randomized to the MSB11456 group will be re-assigned to the same treatment with a probability of 1. Patients initially randomized to the EU-approved RoActemra group will be randomly assigned in a 1:1 ratio to receive either MSB11456 or EU-approved RoActemra. Patients who discontinue study drug before or at Week 24 will not be re-randomized at Week 24 and will discontinue the study. Re-randomization will not impact the double-blind nature of the study as blinding will be kept.

7.3 Patient Demographics

If permitted by local regulation, the age at screening, race, ethnicity and sex of the patient are to be recorded in the electronic Case Report Form at the Screening Visit.

7.4 Medical History

Relevant medical history and current medical conditions (excluding rheumatoid arthritis), history of tuberculosis or any treatment for active/latent tuberculosis, previous surgeries, and smoking status, before screening will be recorded in the electronic Case Report Form at the Screening Visit. Note: If a medication was administered for a previous medical history it will be collected in the Concomitant Medication page of the electronic Case Report Form. At the Baseline Visit, medical history will be reviewed and updated to ensure that the patient remains qualified for the study. Significant findings that are observed with an onset date after the patient has signed the Informed Consent Form and that meet the definition of an adverse event must also be recorded in the Adverse Event electronic Case Report Form page.

Relevant medical history/current medical condition data includes all data up to at least 6 months prior to signature of the Informed Consent Form and until the start of study

treatment and all data deemed medically important by the Investigator. Whenever possible, diagnoses and not symptoms will be recorded.

7.5 Rheumatoid Arthritis Medical History/Previous Rheumatoid Arthritis Therapies

The information to be collected and entered in the electronic Case Report Form includes:

- Phenotype, duration and date of first diagnosis of rheumatoid arthritis (by a physician).
- Any previous biologic or non-biologic therapy for rheumatoid arthritis and the reason for discontinuation.

7.6 Physical Examination

A complete physical examination (including general appearance, skin, head/neck, pulmonary, cardiovascular, gastrointestinal, external genitourinary, lymphatic, musculoskeletal system, extremities, eyes [inspection and vision control], nose, throat and neurologic status) will be performed at screening and at subsequent visits as documented in the Schedule of Assessments (Table 1), and the abnormal results documented in the electronic Case Report Form. All clinically significant abnormalities occurring before signature of informed consent should be recorded in the Medical History and/or Disease History page of the electronic Case Report Form. All clinically significant abnormalities occurring or worsening after signature of informed consent should be recorded in the Adverse Events electronic Case Report Form page. Abnormal findings are to be reassessed at subsequent visits.

Body weight will be assessed together with the physical examination. Body weight will be recorded at screening, baseline and at subsequent visits as indicated in the Schedule of Assessments (Table 1) and documented in the electronic Case Report Form. Height and body mass index will be measured/calculated at the Screening Visit only.

7.7 Vital Signs

Vital signs (including body temperature, respiratory rate, heart rate [after a 5 minute rest], and arterial blood pressure [after a 5 minute rest]) will be measured using a validated device and will be recorded at the Screening Visit and throughout the study at the visits indicated in the Schedule of Assessments (Table 1).

Axillary body temperature measurement will be performed first and will precede every other assessment of each visit. In the case of an elevated temperature, it is the

Investigator's decision to determine any further actions according to local practice and their medical judgment.

After the patient has been sitting for 5 minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using a validated device, with an appropriately sized cuff.

During the study, measurement of vital signs may be repeated at the discretion of the Investigator for safety reasons.

7.8 Imaging

A bidirectional chest X-ray obtained within 3 months prior to randomization will be used to determine eligibility. If patients do not have a bidirectional chest X-ray available within 3 months of randomization, a bidirectional chest X-ray must be done prior to randomization after it is fairly certain the patient meets the other inclusion/exclusion criteria in order to minimize unnecessary exposure to X-ray radiation for patients. If the chest X-ray evaluated by a qualified physician shows evidence of any malignant process, ongoing infectious disease or of an inactive (latent) tuberculosis, the patient will not be eligible to enter the study.

7.9 12-Lead Electrocardiogram

Computerized 12-lead electrocardiogram recordings will be obtained at the Screening Visit after the patient has been supine for 5 minutes. Heart rate, P wave, PR-interval, QRS-wave, QT-interval, and corrected QT intervals (msec) will be recorded from the 12-lead electrocardiogram into the electronic Case Report Form. A copy of the electrocardiograms will be retained at the study center. For the purposes of screening, the Investigator or a designee will evaluate whether the electrocardiogram is normal or abnormal and if abnormal whether it is clinically acceptable for inclusion. Post-randomization, the Investigator or a designee will evaluate whether the electrocardiogram is normal or abnormal, and if abnormal whether it is clinically significant. Abnormal clinically significant 12-lead electrocardiogram results will be documented in the electronic Case Report Form.

The 12-lead electrocardiogram will be repeated at Week 24, Week 52, at the Early Termination and at the final Week 63 End of Study Visit. The electrocardiogram will be repeated at the Safety Follow-Up Visit at Week 55 only if in the opinion of the Investigator it is clinically warranted (e.g., supported by corresponding signs and symptoms).

7.10 Assessment of Efficacy

Efficacy related assessments will be performed at the time points indicated in the Schedule of Assessments (Table 1). All efficacy assessments will be performed before study drug administration.

Rheumatoid arthritis efficacy measures will include DAS28-ESR, DAS28-CRP, ACR Response Criteria (Appendix V), SDAI and CDAI. The efficacy assessments are Tender Joint Count, Swollen Joint Count, Patient's Assessment of Arthritis Pain (Appendix VII), Patient's Global Assessment of Disease Activity (Appendix VIII), Physician's Global Assessment of Disease Activity (Appendix IX) and Health Assessment Questionnaire-Disability Index (Appendix X).

At each time point for rheumatoid arthritis assessments, the Patients Global Assessment of Disease Activity, Patient's Assessment of Arthritis Pain, Health Assessment Questionnaire-Disability Index and Physician's Global Assessment of Disease Activity, will be completed. These assessments should be the first assessments performed at the visits for which they are scheduled right after body temperature measurement.

At these same time points for rheumatoid arthritis assessments, joints will be assessed and classified as swollen/not swollen and tender/not tender by pressure and joint manipulation on physical examination. Joint prosthesis, arthrodesis, or fused joints will not be assessed for swelling or tenderness. The joints to be assessed for swelling and tenderness are given in Appendix V, including the 66/68 joint set for ACR Response Criteria and the DAS28. Appendix VI presents the list of 28 joints used for DAS28, CDAI and SDAI.

7.10.1 Rheumatoid Arthritis Efficacy Measurements

7.10.1.1 Disease Activity Score-28 Joint Count Erythrocyte Sedimentation Rate

The DAS28-ESR is a measure of disease activity in 28 joints that consists of a composite numerical score of the following variables: Tender Joint Count, Swollen Joint Count, erythrocyte sedimentation rate and Patient's Global Assessment of Disease Activity (Appendix VIII).

For DAS28-ESR, the 28 joints to be examined and assessed as tender or not tender for Tender Joint Count and to be examined and assessed as swollen or not swollen for Swollen Joint Count include 14 joints on each side of the patient's body: two shoulders, two elbows, two wrists, ten metacarpophalangeal joints, two interphalangeal joints of the thumb, eight proximal interphalangeal joints and two knees (Smolen, 1995 [12] and Appendix VI).

DAS28 will be derived using the following formula from the DAS28 website (http://www.das-score.nl/)

$$DAS28 = 0.56*\sqrt{(TJC28)} + 0.28*\sqrt{(SJC28)} + 0.014*GH + 0.70*ln(ESR)$$

Where:

- TJC28 = 28 joint count for tenderness.
- SJC28 = 28 joint count for swelling.
- ln(ESR) = natural logarithm of ESR.
- GH = the general health component of the DAS (i.e., Patient's Global Assessment of Disease Activity on a scale of 1 to 100 where 100 is maximal activity).

Abbreviations: SJC28=28–Swollen Joint Count; TJC28=28–Tender Joint Count; ESR=erythrocyte sedimentation rate; GH=General Health

The level of disease activity can be interpreted as:

- Remission (DAS28 score of <2.6).
- Low (DAS28 score of ≤2.6 to <3.2).
- Moderate (DAS28 score of ≤3.2 to ≤5.1).
- High (DAS28 score of >5.1) (Fransen, 2005 [13]).

7.10.1.2 Disease Activity Score-28 Joint Count C-Reactive Protein

The DAS28-CRP is a measure of disease activity in 28 joints that consist of a composite numerical score of the following variables: Tender Joint Count, Swollen Joint Count, C-reactive protein and Patient's Global Health Assessment of Disease Activity as follows (Appendix VIII):

$$DAS28\text{-}CRP = 0.56*\sqrt{(TJC28)} + 0.28*\sqrt{(SJC28)} + 0.36*\ln(CRP+1) + 0.014*GH + 96$$

Where:

TJC28 = 28 joint count for tenderness.

SJC28 = 28 joint count for swelling.

Abbreviations: SJC28=28–Swollen Joint Count; TJC28=28–Tender Joint Count; CRP=C-reactive protein; GH=General Health of the DAS (i.e., Patient's Global Assessment of Disease Activity on a scale of 1 to 100 where 100 is maximal activity) (van Gestel et al, 1998 [14]).

The EULAR Boolean-based response criteria definition:

At any timepoint, a patient must satisfy all of the following:

- Tender joint count ≤1.
- Swollen joint count ≤1.
- C-reactive protein ≤1 mg/dL.
- Patient Global Assessment ≤1 (on a 0-10 scale).

7.10.1.3 American College of Rheumatology Response Criteria

ACR20 (50/70) response criteria (Appendix V) is a dichotomous endpoint indicating the proportion of patients with at least 20 (50,70)% improvement in the number of tender and swollen joints (68/66 joint counts) and at least a 20%/50%/70% improvement in three or more of the five ACR Core Set measures, Patient's Assessment of Arthritis Pain, Physical Function Assessment (Health Assessment Questionnaire-Disability Index), acute phase reactant level (erythrocyte sedimentation rate or C-reactive protein), Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity. Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity will be recorded using a Visual Analog Scale (0-100 mm) as described below in Section 7.10.2.2, Section 7.10.2.3 and Section 7.10.2.4.

The ACR20 is an efficacy measure for which a patient must have at least 20% improvement in the following ACR Core Set values:

- Tender Joint Count (68 joint count).
- Swollen Joint Count (66 joint count).
- An improvement of at least 20% in at least three of the following five assessments:
  - Patient's Global Assessment of Disease Activity.
  - Patient's Assessment of Arthritis Pain.
  - Patient's Assessment of Physical Function as measured by the Health Assessment Questionnaire-Disability Index.
  - Physician's Global Assessment of Disease Activity.
  - Acute phase reactant as measured by erythrocyte sedimentation rate or C-reactive protein.

In this study, ACR20 response calculations will use the Health Assessment Questionnaire -Disability Index for the patient's assessment of physical function and C-reactive protein as the measure of acute phase reactant (C-reactive protein or erythrocyte sedimentation rate).

ACR50 = 50% improvement in at least three of the five measures and 50% improvement in the Swollen and Tender Joint Count.

ACR70 = 70% improvement in at least three of the five measures and 70% improvement in the Swollen and Tender Joint Count.

The ACR response is to be assessed at the visits/time points shown in Schedule of Assessments (Table 1).

7.10.1.4 Simplified Disease Activity Index

The SDAI includes five items:

- 28–Swollen Joint Count.
- 28–Tender Joint Count.
- Patient's Global Assessment of Disease Activity on a Visual Analog Scale.
- Physician's Global Assessment of Disease Activity on a Visual Analog Scale.
- C-reactive protein level in mg/dL.

The SDAI score is calculated by adding the five items together:

SDAI = 28SJC + 28TJC + PGA+ MDGA + CRP.

Abbreviations: 28SJC=28–Swollen Joint Count; 28TJC=28–Tender Joint Count; CRP=C-reactive protein; PGA=Patient's Global Assessment of Disease Activity; MDGA=Physician's Global Assessment of Disease Activity; SDAI=Simplified Disease Activity Index

Appendix VI presents the list of 28 joints used for SDAI.

The level of disease activity can be interpreted as:

- Remission (SDAI score of ≤3.3).
- Low (SDAI score of >3.3 to ≤11).
- Moderate (SDAI score of >11 to ≤26).
- High (SDAI score of >26) (Aletaha, 2005 [11]).

7.10.1.5 Clinical Disease Activity Index

The CDAI includes four items:

- 28–Swollen Joint Count.
- 28–Tender Joint Count.
- Patient's Global Assessment of Disease Activity on a Visual Analog Scale.

- Physician's Global Assessment of Disease Activity on a Visual Analog Scale.

The CDAI is calculated by adding the four items together:

CDAI=28SJC+28TJC+PGA+MDGA.

Abbreviations: 28SJC=28–Swollen Joint Count; 28TJC=28–Tender Joint Count; CDAI=Clinical Disease Activity Index; PGA=Patient's Global Assessment of Disease Activity; MDGA=Physician's Global Assessment of Disease Activity

Appendix VI presents the list of 28 joints used for CDAI.

The level of disease activity can be interpreted as:

- Remission (CDAI score of ≤2.8).
- Low (CDAI score of >2.8 to ≤10).
- Moderate (CDAI score of >10 to ≤22).
- High (CDAI score of >22) (Aletaha, 2005 [11]).

7.10.2 Patient-Reported Measures

Patient-reported outcomes and the Physician's Global Assessment of Disease Activity must be completed right after body temperature measurement before any other assessments at all relevant visits (see Table 1).

7.10.2.1 Health Assessment Questionnaire – Disability Index

The Health Assessment Questionnaire-Disability Index is a self-reported validated questionnaire which assesses the degree of difficulty a patient has experienced during the past week (Fries, 1980 [15]; Bruce, 2005 [16] and Appendix X). It is sensitive to change and is a good predictor of future disability and costs.

The Health Assessment Questionnaire-Disability Index is a questionnaire on which patients are asked to rate their level of difficulty on daily activities (dressing and grooming, arising, eating and walking) and personal abilities (hygiene, reach, grip and activity), as well as their use of aids, devices, or help from another person for these activities and disabilities.

It includes 20 questions organized into eight domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip and other activities.

The Health Assessment Questionnaire-Disability Index is scored from 0 to 3 with higher scores indicating greater disability:

- 0 = no difficulty.
- 1 = some difficulty.
- 2 = much difficulty.
- 3 = unable to do.

The Health Assessment Questionnaire score is the mean of the highest score in each of the eight categories.

7.10.2.2 Patient's Assessment of Arthritis Pain

The patients' assessment of their current level of pain due to arthritis on a 100 mm horizontal Visual Analog Scale (Appendix VII). The left-hand extreme of the line should be described as ''no pain'' and the right-hand extreme as ''severe''.

7.10.2.3 Patient's Global Assessment of Disease Activity

The patient's overall assessment of their disease activity in the past week on a 100 mm Visual Analog Scale (Appendix VIII). The left-hand extreme of the scale will be described as ''very well'' and the right-hand extreme as ''very poorly''.

7.10.2.4 Physician's Global Assessment of Disease Activity

The physician' assessment of the patient's current disease activity on a 100 mm Visual Analog Scale (Appendix IX). The left-hand extreme of the scale will be described as ''no disease activity'' and the right-hand extreme as ''maximum disease activity''.

7.11 Assessment of Safety

The nature, severity and frequency of suspected adverse drug reactions in patients who receive MSB11456 will be compared with those who receive EU-approved RoActemra.

An assessment of any untoward medical occurrences or forewarning indicators thereof experienced by each patient will be performed from the time of giving informed consent and throughout the study. The Investigator will record and report any adverse events occurring after signing the Informed Consent Form, whether observed by the Investigator or reported by the patient.

Other safety assessments to be performed throughout the study are detailed in the Schedule of Assessments (Table 1) and include physical examination, vital signs, 12-lead electrocardiogram, injection site reactions and laboratory tests including clinical chemistry and hematology. Pregnancy testing will be performed as shown in Table 1. Adverse events and concomitant medication will be recorded at each visit.

Assessment of lipid parameters will be monitored routinely after initiation of study treatment according to the Schedule of Assessments (Table 1).

Absolute neutrophil and platelet counts will be monitored throughout the study. For recommended dose modifications based on absolute neutrophil counts and platelet counts (see Section 8.6).

Alanine aminotransferase and aspartate aminotransferase levels will be monitored throughout the study (Table 1). For recommended modifications based on transaminases (see Section 8.6).

Pre-specified adverse events of special interest are provided in Section 10.5.

7.12 Clinical Laboratory Assessments

The hematology, clinical chemistry, lipid panel assessments, follicle-stimulating hormone (women only), viral serology, rheumatoid factor, anti-cyclic citrullinated peptide, QuantiFERON®-TB Gold Plus test, anti-nuclear antibodies, anti-double-stranded DNA, will be performed at a central laboratory. Blood samples will be collected and sent to the central laboratory. In the case that usage of the central laboratory is limited due to unforeseen changes in the COVID-19 situation, certain safety assessments may be performed at a local laboratory with the pre-approval of the Sponsor. The Investigator should assess the available results with regard to clinically relevant abnormalities. Safety laboratory results should be signed and dated and retained at the Investigator's site as source data for laboratory variables.

Urine pregnancy testing and erythrocyte sedimentation rate assessments will be performed locally. Urine pregnancy tests, urine dipsticks and erythrocyte sedimentation rate kits will be supplied by the central laboratory. Urine dipstick will be performed by the Investigator at the site and in the case of an abnormal dipstick finding, a full urinalysis may be performed centrally at the discretion of the Investigator.

Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site (Refer to the Laboratory Manual for full details).

Additional tests may be performed at any time during the study as deemed necessary by the Investigator or required by local regulations. Investigators must document their review of each Laboratory Safety Report.

The following laboratory variables will be measured as shown in Table 3.

Table 3 Clinical Laboratory Assessments

Hematology	White blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration, platelet count, erythrocyte sedimentation rate, neutrophils (absolute and percentage), lymphocytes (absolute and percentage), monocytes (absolute and percentage), eosinophils (absolute and percentage) and basophils (absolute and percentage).
Clinical Chemistry	Sodium, potassium, blood urea nitrogen, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, follicle-stimulating hormone, gamma-glutamyl transferase, lactate dehydrogenase, serum albumin, calcium, phosphate, glucose, creatine kinase, uric acid, total bilirubin, total serum protein and C-reactive protein.
Coagulation:	Activated partial thromboplastin time and prothrombin time.
Lipid Panel	Total cholesterol, triglycerides, high density lipoprotein and low density lipoprotein.
Urinalysis	Dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, Ph, protein, specific gravity and urobilinogen. Full urinalysis (dipstick plus microscopic evaluation) at the Investigator's discretion only if warranted by an abnormal dipstick finding.
Viral Serology	Hepatitis B virus surface antigen, hepatitis B virus core antibody and hepatitis C virus antibody, HIV-1 and HIV-2.
Other	Pregnancy test (women of childbearing potential only), rheumatoid factor, anti-citrullinated protein antibodies, anti-nuclear antibodies, anti-double-stranded DNA and QuantiFERON®-TB Gold Plus tuberculosis test.

Immunogenicity and pharmacokinetic assessments will be performed by a bioanalytical laboratory under the monitoring of Fresenius Kabi SwissBioSim GmbH.

7.12.1 Clinical Chemistry, Hematology, Urinalysis, C-Reactive Protein, Erythrocyte Sedimentation Rate and Lipid Panel

Screening Period

At the Screening Visit, blood samples will be collected for clinical chemistry, hematology, C-reactive protein (as part of the SDAI and DAS28-CRP), erythrocyte sedimentation rate (as part of DAS28-ESR) and lipids. Blood samples will also be taken for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody and HIV-1/HIV-2 testing.

Note: Erythrocyte sedimentation rate will be read at 1 hour after placing the blood in the standardized tube. The 1 hour reading will be used to calculate DAS28-ESR.

Core Treatment Period and Extended Treatment Period

Blood samples will be collected during the study drug administration period for determination of hematology, clinical chemistry, C-reactive protein, erythrocyte sedimentation rate and lipids. Additional unscheduled serum chemistry samples can be collected from those patients who receive anti-fungal drugs or any other medication with known liver toxicity during the study treatment phase (Table 1).

Safety Follow-Up and End of Study Visit

Blood samples will also be taken at the Safety Follow-Up Visit at Week 55 (4 weeks after the last dose [± 7 days] of the study drug) and the End of Study Visit at Week 63 (12 weeks after the last dose [± 7 days] of the study drug) for determination of hematology, clinical chemistry and lipid panel.

7.12.2 Follicle-Stimulating Hormone Test

Blood samples will be taken to measure follicle-stimulating hormone levels at the Screening Visit only. A central laboratory will analyze follicle-stimulating hormone levels.

7.12.3 Pregnancy Test

A serum beta-human chorionic pregnancy test will be performed for women of childbearing potential at the Screening Visit. A urine pregnancy test will be performed during the treatment period.

Urine pregnancy tests will be carried out as stated in Table 1.

Urine pregnancy tests will be supplied by the central laboratory. Urine pregnancy tests will be performed locally. When there is no site visit, the patients will perform the urine pregnancy tests at home every 4 weeks. In the case of a positive urine pregnancy test the patient must immediately notify the Investigator.

7.12.4 Urinalysis

Urine dipstick screening will be performed at the site to determine eligibility (Table 1). Urine samples will be collected during the study treatment phase, at the Safety Follow-Up Visit at Week 55 (4 weeks after the last dose [± 7 days] of the study drug) and the End of Study Visit at Week 63 (12 weeks after the last dose [± 7 days] of the study drug) for the determination of urinalysis. In the case of clinically relevant abnormal urine dipstick findings, a urine sample will be sent to the central laboratory.

7.12.5 Viral Serology

Hepatitis B virus surface antigen, hepatitis B virus core antibody and hepatitis C virus antibody, HIV-1 and HIV-2 will be measured as shown in Table 1. Note: Reflex testing for hepatitis C virus RNA and hepatitis B virus DNA is allowed if hepatitis C virus antibodies or hepatitis B virus antibodies are present without a positive result for hepatitis B virus surface antigen.

7.12.6 Rheumatoid Factor, Anti-Cyclic Citrullinated Protein Antibodies, Anti-Nuclear Antibodies, Anti-Double-Stranded DNA

Rheumatoid factor, anti-cyclic citrullinated peptide antibodies, anti-nuclear antibodies and anti-double-stranded DNA will be assessed as shown in Table 1.

7.12.7 Tuberculosis QuantiFERON® – Gold Plus Test

Patients will be screened for tuberculosis.

Patients with a history of tuberculosis or medical evidence of currently active or latent tuberculosis as indicated by a positive QuantiFERON®-TB Gold Plus test, a chest X-ray and/or a clinical examination are excluded from participating in the study.

Patients will be screened for latent tuberculosis infection by the QuantiFERON®-TB Gold Plus test and by chest X-ray. If a patient tests positive for latent tuberculosis infection at screening, the patient will be screen failed and will not be eligible for participation in the study. If the QuantiFERON®-TB Gold Plus test is indeterminate, patients may be retested once within the Screening Period:

- If the retest is negative, the patient is eligible to participate in the study.

- If the retest is positive, the patient is not eligible to participate in the study.

- If the retest is again indeterminate, the patient is considered as having latent tuberculosis infection and is not eligible to participate in the study. No further QuantiFERON®-TB Gold Plus testing will be performed.

Study drug will be discontinued in patients who were QuantiFERON®-TB Gold Plus test negative at randomization, but subsequently become QuantiFERON®-TB Gold Plus test positive at Week 24. Patients whose QuantiFERON®-TB Gold Plus test is indeterminate at Week 24 may be retested once. If on retest the result is positive or indeterminate then the patient must be withdrawn from the study. The QuantiFERON®-TB Gold Plus test need not be repeated if the patient has had a QuantiFERON®-TB Gold Plus test performed within 4 weeks before the Early Termination Visit.

7.13 Local Tolerability

Local tolerability (injection site reactions) will be assessed by inspection of the skin and appendages in proximity to the site of the injection before and after the injection at the time points specified in the Schedule of Assessments (Table 1). This local tolerability assessment will be performed by the Investigator or designee to determine the presence of e.g., erythema, rash, tenderness, swelling, itching, bruising, pain, or other abnormalities. The Investigator is also requested to ask patients during this assessment about any such reactions that may have occurred since the last such assessment. All such findings including the time of onset and resolution as well as the need for ancillary care will be recorded in the source data and transferred into the corresponding dedicated electronic Case Report Form page. Non-serious injection site reactions are only to be reported in this dedicated electronic Case Report Form page and not on the Adverse Event Case Report Form page. Injection site reactions that qualify as serious adverse events (e.g., ulceration that leads to or prolongs hospitalization, see Section 9.2) or meet the definition of an adverse event of special interest (see Section 10.5) must be recorded as a serious adverse event or an adverse event of special interest (as applicable) on the corresponding page of the electronic Case Report Form. The Investigator is asked to assess the relatedness of the injection site reactions to the study drug and to grade the severity of all injection site reactions according to the latest version of the National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE).

Any injection site reaction reported by the patient following study drug administrations performed at home shall also be recorded in the dedicated Injection Site Reaction electronic Case Report Form page.

7.14 Immunogenicity

Serum immunogenicity samples will be collected at the time points specified in the Schedule of Assessments (Table 1) to determine the incidence of antidrug antibodies and to further characterize positive samples. Blood samples for immunogenicity assessments must be drawn prior to the administration of the study drug, which will be performed at the site for these visits. Separate samples will be collected for antidrug antibody and neutralizing antidrug antibody assessments.

The assay strategy is based on a multi-tiered approach. In the first tier, all samples will be assessed using a screening assay. In the second tier, samples testing putative positive in the screening assay will then be analyzed in a confirmatory assay. Samples that are positive in the confirmatory assay will then be further characterized to determine the antidrug antibody titers. Finally, in the third tier, all confirmed positive samples will be tested in a neutralizing antidrug antibody assay to determine if antidrug antibodies against the drug are neutralizing the biological activity.

Antidrug antibody assays will be performed by a bioanalytical laboratory under the responsibility of Fresenius Kabi SwissBioSim GmbH using methods validated according to regulatory guidelines. Immunogenicity assessments will be described in the bioanalytical plans, which will be finalized before the beginning of sample analysis. Bioanalytical reports will also be generated, one for each antidrug antibody and neutralizing antidrug antibody analysis, by the bioanalytical laboratory and will be included in the Clinical Study Report (CSR) appendix.

After completion of the study, immunogenicity samples will be stored for a maximum of 10 years as from the last patient's last visit in this study at the designated storage facility meeting the below requirements:

- Utilize Good Clinical Practice (GCP)-compliant sample management system.
- Perform GCP-compliant receipt and storage of biosamples.
- Perform GCP-compliant outbound shipment of biosamples.
- Perform GCP-compliant destruction of biosamples (if requested).

The immunogenicity samples will be processed, shipped and stored as described in the Laboratory Manual.

7.15 Pharmacokinetics

For both the main study and the sub-study, the exact date and time of the blood sample collection must be recorded in the source document and transcribed into the patient's electronic Case Report Form. Actual sampling times will be used in the calculation of pharmacokinetic parameters. In the event that the actual time is not recorded, the scheduled sampling time will be used. The exact date and time of study drug dosing must also be recorded.

After completion of the study, pharmacokinetic samples will be stored for a maximum of 10 years as from the last subject's last visit in this study at the designated storage facility meeting the below requirements:

- Utilize GCP-compliant sample management system.
- Perform GCP-compliant receipt and storage of biosamples.
- Perform GCP-compliant outbound shipment of biosamples.
- Perform GCP-compliant destruction of biosamples (if requested).

Refer to the Laboratory Manual for full details for sample handling and storage of pharmacokinetic samples.

7.15.1 Pharmacokinetics Main Study

During the main study, the pharmacokinetic trough study drug concentration sampling will be performed (see Table 1).

A pharmacokinetic trough concentration sample will be collected from all patients in conjunction with the immunogenicity sampling (Table 1). This sample must be collected prior to the immunogenicity sampling and prior to the study drug administration. The determination of pharmacokinetic trough study drug concentration will be performed for all patients in the main study using a validated method by a bioanalytical laboratory under the responsibility of Fresenius Kabi SwissBioSim GmbH. Analysis methods will be defined in a Bioanalytical Protocol and the results will be reported in a Bioanalytical Report.

7.15.2 Pharmacokinetics Sub-Study

Patients may be asked to participate in a population pharmacokinetic sub-study performed during the 24-week Core Treatment Period (Day 1 to Day 169/Week 24).

Patients must give written informed consent that they agree to participate in the population pharmacokinetic sub-study.

During the population pharmacokinetic sub-study additional blood samples will be taken at time points shown in Table 2 for the measurement of tocilizumab concentrations in order to characterize pharmacokinetics of both products.

The sample size for the population pharmacokinetic sub-study will be in a subset of approximately 30 patients per group, for a total of up to 60 patients (to ensure that approximately 50 patients complete the pharmacokinetic sub-study).

The sparse blood sample collection time points were derived from a previously published model (Abdallah, 2017 [5]; Actemra® Food and Drug Administration [FDA] BLA 125472 [17]) using an optimal sampling schedule analysis (D'Argenio, 2009 [18]).

7.16 Protocol Deviations

Protocol deviations include the patient's findings or conduct failing to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment non-compliance, failure to return for defined number of visits). The deviation should be discussed with the Medical Monitor prior to discontinuation of the study drug. Protocol deviations, including their categorization (i.e., important/major protocol deviations) need to be defined to allow for a pro-active and ongoing monitoring and management of the observed protocol deviations. All COVID-19 vaccines administered before the completion of the Week 30 visit will be reported as COVID-19-related protocol deviations.

8 STUDY DRUG MANAGEMENT

8.1 Description

The study drugs to be administered in this study are the proposed tocilizumab biosimilar candidate MSB11456 and EU-approved RoActemra.

8.1.1 Formulation

The reference therapy (comparator) is EU-approved RoActemra which is provided in a single-use pre-filled syringe. Each pre-filled syringe contains 162 mg tocilizumab in 0.9 mL sterile liquid solution. The list of excipients of EU-approved RoActemra is provided in the prescribing information.

MSB11456 is provided in a single-use pre-filled syringe. Each pre-filled syringe contains 162 mg MSB11456 in 0.9 mL sterile liquid solution. The formulation of MSB11456 is different to that of EU-approved RoActemra and the list of excipients is provided in the Investigator's Brochure [2].

8.1.2 Handling and Storage of the Investigational Medicinal Product

The study drug must be stored in a secure area with limited access under controlled conditions at 2 to 8°C and protected from light. The study drug must not be frozen and rough shaking of the solution must be avoided.

Prior to use, the pre-filled syringe for both EU-approved RoActemra and MSB11456 should be removed from the refrigerator and kept at room temperature (outside of the carton) for 30 minutes. The pre-filled syringe should not be shaken. If visibly opaque particles, a change of color or other foreign particles are observed, the solution should not be used. Any study drug that has been stored improperly must not be dispensed to any patient before it has been re-evaluated and approved for further use by responsible personnel. Improperly stored study drug must be quarantined at the site to ensure that it is not dispensed to patients before re-approval of use has been obtained.

8.2 Blinding of Study Medication

To ensure that the blind of the study drug is maintained, each study drug (MSB11456 and EU-approved RoActemra) syringe will be blinded.

The study will be double-blinded with the patients, the investigators and the Sponsor being blinded to the study drug administered. Randomization data will be kept strictly confidential, accessible only to authorized staff, until the time of unblinding.

Details on who will be unblinded in the context of the Week 30 CSR will be given in a Data Access Plan to be finalized before the Week 30 unblinding will be performed. However, the Sponsor will be unblinded at the time of the Week 30 results.

Breaking of the blinding is only allowed in the case of an emergency, when knowledge of the study drug is essential for the clinical management of the patient. The Investigator must make every effort to contact the CRO Medical Monitor prior to breaking the study blind. Patients whose treatment assignments are unblinded will not receive any further study drug.

Emergency unblinding will be organized through IRT system. If the blind is broken, the Investigator must inform the Sponsor immediately without revealing to the Sponsor the results of the code break, except to the designated Global Patient Safety representative (Emergency Unblinding Notification Form). The Investigator must record the date of unblinding and the reason. All breaks of the study blind must be adequately documented.

If a serious adverse event is reported, the CRO's or Sponsor's Global Patient Safety Department may unblind the treatment assignment for the individual patient through the IRT system. If an expedited regulatory report is required, this report will usually identify the patient's treatment assignment according to regulations. When applicable, an expedited report will be sent to all investigators in accordance with regulations. Code breaks performed at a place other than the study site will also be documented carefully, as per the CRO policies.

8.3 Packaging and Shipment

All study drugs will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

MSB11456 and EU-approved RoActemra will be provided in single-use, pre-filled syringes.

The study drugs will be shipped and stored under controlled conditions according to the storage requirements at 2 to 8°C and protected from light.

8.4 Dose and Administration

The study has two groups:

1. EU-approved RoActemra will be administered at a dose of 162 mg by the subcutaneous route every week starting on the morning of Day 1.

2. MSB11456 will be administered at a dose of 162 mg by the subcutaneous route every week starting on the morning of Day 1.

Prior to administration, the pre-filled syringe should be removed from the refrigerator and should be kept at room temperature (outside of the carton) for approximately 30 minutes before administration.

Once removed from the refrigerator, the injection must be administered within 8 hours and should not be kept above 30°C.

The syringe should not be shaken. After removing the cap, the injection must be started within 5 minutes, to prevent the medicine from drying out and blocking the needle. If the pre-filled syringe is not used within 5 minutes of removing the cap, it must be disposed of in a puncture resistant container and a new pre-filled syringe should be used. If following insertion of the needle the plunger cannot be depressed, then the pre-filled syringe must be disposed of in a puncture resistant container and new pre-filled syringe used.

The study drug will be supplied in single-use syringes and no further preparation is required. The syringes must be kept in the original outer packaging until administration. The preparation should be carefully inspected before injection (it should be a homogenous looking clear solution, free of visible particles). It should be discarded if the solution is any color besides colorless to slightly yellowish, or if any part of the pre-filled syringe appears to be damaged.

The recommended injection sites are the lower part of the abdomen below the navel except for the 5 cm area directly around the navel. Injection sites should be rotated and injections should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

Administration of study drug will be initiated by a healthcare professional experienced in giving subcutaneous injections. If after proper training, the healthcare professional judges it appropriate, the patient (or a trained caregiver) may self-inject the medication. The first three doses of study drug (162 mg at Day 1, Day 8 and Day 15) will be administered on-site to ensure the patient or their caregiver is appropriately trained. The exact date and dosing times of these three doses of study drug will be recorded in the electronic Case Report Form. Patients will be monitored for 2 hours following these first

three doses of study drug. The following weekly doses of study drug can be self-administered if the patient is able to self-administer him/herself at the discretion of the Investigator. Injections must be administered on the same day every week, whenever possible. Study drug will be dispensed and written instructions on proper dosage, administration, storage and recording will be provided to the patient.

Patients will be instructed to measure his/her axillary body temperature before each self-administration and before each time visiting the clinic site.

In the case of body temperature above normal (>37.5°C), the patient should not self-administer the study drug and should contact site staff immediately for further instructions.

In the case of body temperature above normal (>37.5°C) before visiting the clinical site, the patient should contact site staff immediately for further instructions.

Administrations performed at home will be recorded in a diary together with the fact that the body temperature measurement has been performed before the administration and site visits and the body temperature was not >37.5°C. The time of the body temperature measurement will be recorded in the diary. The data collected in the diary will be transferred into the electronic Case Report Form with the accurate dosing information (dosing date and time).

Dispensed study drugs will be returned by the patient at each visit.

During the initial 24-week Core Treatment Period (Day 1 to Day 169/Week 24), patients will receive a total of 24 doses of either EU-approved RoActemra or MSB11456 (one dose of 162 mg at each of Weeks 0 to 23 inclusive) prior to primary endpoint evaluation at Week 24.

During the Extended Treatment Period, patients will receive a total of 28 doses of either MSB11456 or EU-approved RoActemra (one dose of 162 mg at each of Weeks 24 to 51 inclusive).

8.5 Missed Investigational Medicinal Product Dose

If for any reason the weekly study drug injection cannot be administered on the scheduled day, a 5-day minimum and a 9-day maximum interval between injections is acceptable (calculated based on the day of the scheduled dose, not from the date of the last injection). Outside of this minimum maximum window, the dose will be counted as a missed dose and the patient should be instructed to take the next planned dose at the next planned day. All missed doses of study drug at site must be recorded in the electronic Case Report Form. All missed doses of study drug taken at home must be recorded into

the diary and will be transferred into the electronic Case Form. Adequate compliance (at least 80% for the first 24 weeks of treatment) and sufficient exposure to study medication is expected from each patient ensuring adequacy and completeness of data being collected.

8.6 Investigational Medicinal Product Dose Modifications

Treatment with study drug may be interrupted due to low absolute neutrophil count, low platelet counts, abnormalities in liver or any other toxicity that requires interruption of study drug treatment in the opinion of the Investigator (see RoActemra® EU Summary of Product Characteristics, 2019 [1]). Medical care for any toxicities will be provided as per institutional standards as required. If study drug cannot be resumed and/or in case of toxicity that unacceptably endangers the safety of the patient in the opinion of the Investigator, the patient should be discontinued from treatment. Unless not justifiable, all patients discontinuing treatment should be encouraged to remain in the study and participate in the subsequent scheduled visits. All dose modifications of study drug and concomitant medications including methotrexate must be recorded in the electronic Case Report Form.

Low Absolute Neutrophil Counts

Dosing with study drug should be interrupted in patients with absolute neutrophil count 0.5 to 1 cells x 10^9/L. When absolute neutrophil count increases to >1 x 10^9/L, treatment with study drug can be resumed, as clinically appropriate.

Dosing with study drug should be permanently discontinued in patients with two successive absolute neutrophil count measurements <0.5 cells x 10^9/L.

Low Platelet Count

Dosing with study drug should be interrupted in patients with 50 to 100 cells x 10^3/µL. When platelet count increases >100 x 103/µL treatment with study drug can be resumed, as clinically appropriate.

Dosing with study drug should be permanently discontinued in patients with two successive platelet counts <50 x 10^3/µL.

Liver Enzymes

In patients with liver enzymes (i.e., alanine aminotransferase and aspartate aminotransferase) >1 to 3 x ULN, the dose of concomitant methotrexate and/or non-steroidal anti-inflammatory drugs or other potentially hepatotoxic concomitant medications should be modified if appropriate. For persistent increases (i.e., the liver

enzyme elevation persists even after modification of concomitant methotrexate and/or non-steroidal anti-inflammatory drugs or other potentially hepatotoxic concomitant medication) increases in this range, the study drug dose frequency should be reduced to every other week injection or interrupted until alanine aminotransferase or aspartate aminotransferase have normalized. Weekly injections can be resumed, as clinically appropriate i.e., liver enzyme levels are within the normal ranges or at baseline no clinical or other diagnostic signs or hepatic impairment/disease and based on the discretion of the Investigator would not pose an additional risk to the patient.

In patients with liver enzymes (i.e., alanine aminotransferase and aspartate aminotransferase) >3 to 5 x ULN, dosing of study drug should be interrupted until <3 x ULN and the recommendations above for >1 to 3 x ULN should be followed. For persistent increases >3 x ULN (confirmed by repeat testing and/or three or more missed doses of study drug for elevated liver function tests), study drug should be permanently discontinued.

If a recurrent increase in liver enzymes (i.e., alanine aminotransferase and aspartate aminotransferase) occurs at any time after an initial drop to <3 x ULN, study drug should be discontinued.

Dosing with study drug should be discontinued in patients with liver enzymes >5 x ULN.

If three consecutive doses or more are missed due to alanine aminotransferase/aspartate aminotransferase elevations, study drug should be discontinued.

Bilirubin

The study drug should be discontinued if indirect bilirubin increases to ≥2 x ULN.

Potential Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of alanine aminotransferase or aspartate aminotransferase ≥3 x ULN together with total bilirubin ≥2 x ULN must be followed-up by an immediate re-testing of the values and if confirmed in a second test must be reported as serious adverse events and study drug must be put on hold. The [redacted] must be consulted immediately of the event to discuss further action. This would require further assessment for potential Hy's Law event.

Serious Infections

Administration of study drug should be interrupted if a patient develops a serious infection until the infection is controlled. Following discussion with the Medical Monitor and with his/her agreement, treatment should be re-introduced in these patients when the infection is controlled and no disproportionate risk to the patient is anticipated if re-exposed to the study drug.

COVID-19 Infection

Administration of study drug should be interrupted if a patient has known SARS-CoV-2 exposure (even without symptoms related to COVID-19). Treatment with study drug can be re-introduced if the patient tests negative for COVID-19 or after 2 weeks of symptom-free observation.

Administration of study drug should be interrupted if a patient has documented or presumptive COVID-19 infection until the patient is recovered. Treatment with study drug can be re-introduced in line with local practice following the recovery of the patient and following discussion with the Medical Monitor and with his/her agreement.

Any local site policy or local government policy supersedes above guidance.

8.7 Interaction with Other Medicinal Products

The expression of hepatic CYP450 enzymes is suppressed by cytokines, such as interleukin-6, that stimulate chronic inflammation. Thus, CYP450 expression may be normalized when potent cytokine inhibitory therapy, such as tocilizumab, is initiated. When starting or stopping therapy with study drug, patients taking medicinal products which are metabolized by cytochrome enzymes for example CYP450 3A4, 1A2 or 2C9 (e.g., atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin or benzodiazepines) should be monitored as doses may need to be increased to maintain therapeutic effect.

8.8 Accountability

The study drug must not be used for purpose other than those defined in this Clinical Study Protocol. All supplies of study drug will be accounted for in accordance with GCP. There will be a master study drug accountability record completed, and the pharmacist, or designee, should maintain accurate records of the disposition of all study drug supplies received during the study. These records should include the amounts and dates that study drug were received and destroyed/returned to the Sponsor or its designee. If errors or damages in the study drug shipments occur, the Investigator should contact the applicable depot immediately.

In addition to the master study drug accountability form, the site must use the patient level study drug accountability logs which will account for the study drug provided to the patients for self-injection in between on-site clinical visits. The patient level study drug accountability will:

- Record the date, patient number, the study drug number dispensed.
- Record the date, quantity of used and unused study drugs returned, along with the initials of the person recording the information.

Study drugs will be reconciled using syringe carton count at every patients' on-site clinical visits by the Investigator or designee (i.e., pharmacist) in order to monitor the patient's adherence with the study drug regimen.

Copies of the study drug accountability records will be provided by each Investigator for inclusion in the Trial Master File. The study monitor will periodically check the supplies of study drug held by the Investigator or pharmacist to verify accountability of study drug used.

The Investigator (or designee) will administer and hand out the study drug only to the identified patients of this study, according to the procedures described in this Clinical Study Protocol. After the end of the study, all unused study drug and all medication containers should be destroyed at the study center or returned to the Sponsor or its designee. In either instance, complete documentation will be returned to the Sponsor. The study drug re-supply will be managed by the IRT system.

8.9 Pre-Study Medications

Use of pre-study medication must be recorded as comprehensively as possible. Methotrexate use including dose and route of administration prior to randomization must be recorded. All pre-study medications including disease-modifying anti-rheumatic drug history and all targeted therapies (i.e., biologics, small molecules) to which the patient was ever exposed must be recorded, including duration of treatment.

It is recommended that all patients be brought up to date with all immunizations according to vaccination local practice prior to initiating treatment with the study drug. If this condition is not met, the patient will still be eligible to participate in the study if they meet the inclusion (Section 5.2) and exclusion criteria (Section 5.3).

8.10 Concomitant Medications and Procedures

At each visit, all concomitant medications taken by the patient during the study from the date of signature of informed consent up to the completion of the final End of Study Visit

are to be recorded in the appropriate section of the electronic Case Report Form, noting the name (generic and Tradename), dose/frequency/route, start/stop dates, duration and indication of each drug. Non-drug interventions and any changes to a concomitant medication or other intervention should also be recorded in the electronic Case Report Form. Any COVID-19 vaccination must be recorded on the Concomitant Medication page of the electronic Case Report Form including all available data (Tradename, manufacturer/Marketing Authorization Holder, date and time of vaccination and batch number whenever available).

8.11 Permitted Medicines

Any medications, therapies, or procedures (other than those excluded by the Clinical Study Protocol) that are considered necessary to protect patient welfare and will not interfere with the study drug may be given at the Investigator's discretion. This includes, and is not limited to, initiation of lipid lowering agents according to prevailing local guidelines to ensure adequate control. All permitted medication and dose modifications of permitted medication must be recorded in the electronic Case Report Form. Permitted medication will not be provided by the Sponsor as it is considered standard of care background medication.

While reductions in medication are allowed for safety reasons, it is important that medication dosages taken during the study remain stable to the extent possible.

Methotrexate

To be eligible for the study, all patients must have been treated with methotrexate for at least 12 consecutive weeks immediately prior to randomization and are on a stable dose between 10 and 25 mg/week methotrexate for the last 8 weeks prior to screening. The dose and route of administration of methotrexate at study entry should be continued without change during the study, in particular during the 52-week treatment period of the study. Temporary dose interruptions (up to 14 days or two doses), are allowed during the study for safety reasons. If a patient develops methotrexate-related side effects, a dose reduction(s) or interruption(s) is possible at the Investigator's discretion.

Folic Acid

All patients will receive a stable dose of folic acid (≥5 mg/week folate total dose), either as a single dose or as daily doses according to local guidelines.

Oral Corticosteroids

Oral corticosteroids (≤10 mg/day prednisone or equivalent) are permitted during the study provided the dose had been stable for at least 6 weeks prior to randomization.

Increases in oral corticosteroid dose for the treatment of rheumatoid arthritis are not permitted during the study.

Non-Steroidal Anti-Inflammatories

Non-steroidal anti-inflammatories up to their maximum recommended dose are permitted during the study if the dose had been stable for at least 4 weeks prior to randomization. Dose increases are not permitted during the study, although dose reductions or discontinuations are allowed for safety reasons. Aspirin (dose of ≤325 mg/day) is allowed for cardiac prophylaxis.

Analgesics (Other Than Non-Steroidal Anti-Inflammatories)

Analgesics up to the maximum recommended dose are permitted throughout the study although strongly discouraged within 24 hours prior to a study visit at which efficacy will be assessed. Use of paracetamol is allowed in the study.

Opioid Analgesics

Use of low potency opioid analgesics (codeine, hydrocodone, tramadol and tapentadol) are permitted during the study at doses of no more than 40 mg of morphine equivalent, although strongly discouraged within 24 hours prior to a study visit at which efficacy will be assessed. Use of high potency opioid analgesics (e.g., hydromorphone, oxycodone, fentanyl, or morphine) are not permitted.

Proton Pump Inhibitors and Histamine Subtype-2 Receptor Blockers

All patients receiving non-steroidal anti-inflammatory drugs should be assessed and treated with proton pump inhibitors or histamine subtype-2 receptor blockers at the recommended doses according to the current local standards of care.

Hormone Replacement Therapy

For female patients, hormone replacement therapy is allowed only if the patient was already taking the therapy prior to study entry. Initiating hormone replacement therapy during the study is not permitted. Women whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their hormone replacement therapy during the study.

Over-The-Counter Medications and Supplements

Any concomitant medications (including over-the-counter medications, herbal medications, Chinese medications, vitamins and food supplements) and procedures must be recorded in the electronic Case Report Form.

Procedures

A description of the type of drug or procedure, the dose/amount, duration, reason for administration of drug and the outcome of any procedure must be documented.

Adverse Events Related to Concomitant Medication/Procedures

Adverse events related to the administration of a concomitant medication or the performance of a procedure must also be recorded.

8.12 Prohibited Medications

The use of prohibited medications during the study will require the patient to be permanently discontinued from the study drug. The use of prohibited medications is also not permitted within 4 weeks after the last dose of study drug (i.e., Weeks 51 to 55), during which safety data will be collected. For the period between 4 weeks and 12 weeks after the last dose of study drug, the patient can receive standard of care treatment for rheumatoid arthritis as per the current local guidelines.

Medication may be administered for the treatment of adverse events or emergency treatment at any time during the study and must be recorded in the electronic Case Report Form.

Table 4 presents a summary of prohibited medications with washout periods (before randomization).

Table 4 Summary of Prohibited Medications with Washout Periods (Before Randomization)

Prohibited Medications	**Washout Period (Before Randomization)**
Biological immunomodulating agents >2 different	Never
Biologic treatments not administered for the treatment of rheumatoid arthritis	Never
Biologic treatments for the treatment of rheumatoid arthritis	12 weeks
Alkylating agents, or cell-depleting therapies including investigational drugs or approved biosimilars	Never
Targeted synthetic disease-modifying anti-rheumatic drugs biological agent for a condition other than rheumatoid arthritis	Never
Conventional synthetic disease-modifying anti-rheumatic drugs (except methotrexate)	8 weeks
Leflunomide	12 weeks
Leflunomide with cholestyramine	4 weeks
Unstable dose of non-steroidal anti-inflammatory drugs (cyclooxygenase-1 or cyclooxygenase-2 inhibitors) (until Week 52)	4 weeks
Oral corticosteroids >10 mg prednisone or equivalent (until Week 52)	6 weeks
Unstable dose of oral corticosteroids ≤10 mg prednisone or equivalent (until Week 24)	6 weeks
Intra-articular or parenteral corticosteroid injections (until Week 24)	4 weeks
High potency opioid analgesics (e.g., methadone, hydromorphone, oxycodone, fentanyl, or morphine)	Never
Intravenous gamma globulin or plasmapheresis	6 months
Any investigational treatment or participation in any interventional study	5 half-lives/12 weeks whichever is longer
Live or attenuated vaccinations*	4 weeks
*COVID-19 vaccination-related restrictions are detailed in Section 8.13.	

Administration of These Agents Require Study Drug Discontinuation

Note: As mentioned in Section 6.3, the aim to collect as much as safety and efficacy data from any patient that has discontinued from the study drug. If a patient discontinues study drug prior to Week 24, the patient will remain in the study up to the completion of the Week 24 assessments. If a patient discontinues study drug during the Extended Treatment Period, the patient will be followed-up until the End of Study Visit.

Disease-Modifying Anti-Rheumatic Drugs (Other Than Methotrexate)

The use of disease-modifying anti-rheumatic drugs including biological disease-modifying anti-rheumatic drugs other than the study drugs (methotrexate or MSB11456/EU-approved RoActemra) is not permitted during the study and must be discontinued at least 8 weeks prior to randomization with the exception of leflunomide which must have been discontinued for ≥12 weeks prior to randomization (or ≥4 weeks after 11 days of standard cholestyramine washout), in accordance with the inclusion and exclusion criteria.

Intravenous or Intramuscular Corticosteroids

Treatment with intravenous or intramuscular corticosteroids is not permitted during the study. Oral corticosteroids are permitted as per Section 8.11.

Intra-Articular Corticosteroids

Intra-articular or parental corticosteroids are not permitted within 4 weeks prior to randomization until after the Week 24 assessments for the primary analysis. Intra-articular corticosteroids are discouraged while on study drug during the 24 to 52-week Extended Treatment Period but if absolutely necessary, a single injection not exceeding 40 mg triamcinolone or equivalent can be injected into no more than one joint during the 24 to 52-week period. The joint that is injected must be recorded as non-evaluable in subsequent entries in the electronic Patient-Reported Outcome or electronic Case Report Form.

Intravenous Gamma Globulin or Plasmapheresis

Treatment with intravenous gamma globulin or plasmapheresis is not permitted within 6 months prior to randomization, during the 52-week study and during the 4-week Safety Follow-Up Period after the last dose of study drug.

Vaccinations

Immunization with live or attenuated vaccines is not permitted within 4 weeks prior to randomization, during the 52-week study and during the 4-week Safety Follow-Up Period after the last dose of study drug. Details regarding COVID-19 vaccines are provided below in Section 8.13.

8.13 COVID-19 Vaccinations

Interleukin-6 has an important role in controlling the homeostasis of virus-specific T-follicular helper cells during germinal center responses required to generate high-affinity antivirus antibodies and effective virus-specific memory B-cells following vaccination. Any interference, such as administration of an anti-interleukin-6 antibody like tocilizumab, with the binding of interleukin-6 to its receptor could potentially impact the generation of high-affinity antiviral antibodies and the generation of virus-specific memory B-cell responses. This could potentially impact the efficacy of an antiviral vaccine.

Additionally, vaccination against SARS-Cov-2 infection is expected to activate the innate immune system and may result in increased serum interleukin-6 and other stimulatory factor levels which could have an impact on the disease activity in patients with rheumatoid arthritis and potentially influences the effectiveness of therapeutic antibodies against interleukin-6 receptor, such as tocilizumab thereby jeopardizing the primary objectives of the current clinical study.

Vaccination will also cause a systemic effect on the innate and adaptive immune system (e.g., bystander activation) which could result in an increased propensity of the immune system to generate unwanted antidrug antibody responses (e.g., antidrug antibodies, neutralizing antidrug antibodies) against tocilizumab thereby jeopardizing the effectiveness of current and future tocilizumab treatment of the patient.

Due to the potential interference between study treatment and COVID-19 vaccinations, COVID-19 vaccination is not allowed from 4 weeks prior to randomization until the completion of the Week 30 visit.

Following the completion of the Week 30 visit, taking into consideration the above, COVID-19 vaccination is not recommended until the completion of the Week 55 visit (i.e., 4 weeks after the last study drug dose).

In the case that the patient's vaccination is still planned following the completion of the Week 30 visit, in order to minimize impact on main study objectives, it is advised to perform it right after the Week 30 or Week 42 visits. In order to ensure the development of an adequate immune response provoked by COVID-19 vaccination, it is advised to

interrupt study treatment 1 week before and after each dose of vaccination (i.e., to leave out one or two doses to ensure 7 days of study treatment-free period before and after each dose of vaccine).

Any COVID-19 vaccination must be recorded on the concomitant medication page of the electronic Case Report Form including all available data (Tradename, manufacturer/Marketing Authorization Holder, date and time of vaccination and batch number whenever available).

Adverse Reactions related to vaccination must be recorded using the Adverse Event page of the electronic Case Report Form and clearly indicating that the adverse event is suspected to be related to COVID-19 vaccination.

The administration of COVID-19 vaccine as not allowed medication during the study will not automatically require the patient to be permanently discontinued from the study drug but requires prior discussion with the Medical Monitor of the study and joint decision and agreement of Principal Investigator and Medical Monitor on the continuation of study treatment. All COVID-19 vaccines administered before the completion of the Week 30 visit will be reported as COVID-19-related protocol deviations.

8.14 Management of Specific Adverse Events or Adverse Drug Reactions

Standard medical care will be provided at the site for all adverse events that occur during the study.

Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, hemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly and referred to specialist care for appropriate medical management and to avoid complications such as gastrointestinal perforation. If gastrointestinal perforation occurs, the patient will receive the necessary emergency care, including medical and surgical treatment if required. Gastrointestinal perforations and serious complications of diverticulitis must be reported as adverse events of special interest (see Section 10.5).

8.15 Compliance

The administration of study drug should be recorded in the appropriate sections of the Case Report Form and diary.

Treatment compliance will be assured by site reconciliation of the medication and by diary review. The Investigator will review the patient's diary entry at each study visit so that if they notice any deviations, they can retrain the patient with regards to the protocol dosing schedule.

9 SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

Investigators or other site personnel must inform the Sponsor and CRO immediately (no later than 24 hours) after becoming aware of a serious adverse event, adverse event of special interest, pregnancies or any incidence of overdose.

Electronic Case Report Form reporting (within the Electronic Data Capture system) will be used in this study. When the sites enter data for these events within the electronic Case Report Form, the CRO Safety Department will receive an alert from the system.

In the event that Electronic Data Capture is not available the Investigator or designee can report by fax/email to the contact information provided below in order to comply with the reporting timeframe. Once the Electronic Data Capture is available, it should be updated as soon as possible.

CRO Safety Department contact information:

Email: [redacted]

Fax: [redacted]

9.1 Definition of Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (Guidance for Industry and Investigators [19]).

An adverse event can be any unfavorable and/or unintended sign (including findings from laboratory assessments or technical investigations), symptom, impaired functionality or other clinical manifestation temporally associated with the exposure to the study drug. For surgical or diagnostic measures the triggering medical circumstance(s) such as a sign, symptom or diagnosis is considered the eliciting adverse event. All instances of a new-onset or worsening of a pre-existing condition or untoward medical occurrence qualify as an adverse event and must be reported accordingly. Medical conditions present at the initial study visit that do not change in nature, severity or frequency are defined as Baseline Medical Conditions and are not to be considered adverse events.

Medical conditions/diseases present before starting the investigational drug will be considered adverse events only if they worsen after starting study treatment.

Adverse events do not include the following:

- Pre-planned medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed.
- Not pre-planned medical or surgical procedures are not adverse events but the condition that leads to the procedure can be an adverse event.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visits that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae.
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an adverse event. It is considered to be pre-existing and should be documented on the Medical History Case Report Form.
- Uncomplicated pregnancy (documented on the Pregnancy page of the electronic Case Report Form).
- An induced elective abortion to terminate a pregnancy without medical reason (documented on the Pregnancy page of the electronic Case Report Form).

The term adverse event is used to include both serious and non-serious adverse events.

9.2 Definition of Serious Adverse Events

A serious adverse event is any event that meets any of the following criteria:

- Death.
- Required hospitalization (inpatient treatment) or prolongation of existing hospitalization.
- Is life-threatening. (Note: The term "life-threatening" refers to an event in which the patient is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.).
- Results in persistent or significant disability or incapacity.

- Is a congenital anomaly or birth defect.

- Is otherwise considered to be medically important. (Note: An adverse event may be considered as serious adverse event when, based upon appropriate medical judgment, it may otherwise jeopardize the patient or require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

Suspected transmission of an infectious agent via a study drug also qualifies as a serious adverse event for this study.

Several events classified as serious adverse events may occur simultaneously. In this case, investigators should indicate which of the serious adverse events is the primary event.

Confirmed COVID-19 cases should be considered as 'otherwise medically important' and accordingly reported as serious adverse events.

A clinical adverse event of severity of Grade 4 or higher qualify as a serious adverse event and must be reported accordingly. Findings from laboratory tests or additional investigations of Grade 4 or above are considered serious only if they also meet one of the defined criteria for a serious adverse event.

Elective hospitalization to administer study drug or perform study procedures, or for pre-planned surgery or diagnostic procedures do not qualify as serious adverse event. Unplanned hospitalizations or prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as a serious adverse event.

Definition of Terms

Life-threatening: an adverse event is life-threatening if the patient was at immediate risk of death from the event as it occurred. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug induced hepatitis can be fatal. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death (Guidance for Industry and Investigators [19]).

Hospitalization: adverse events requiring hospitalization should be considered serious adverse events. Hospitalization or elective surgery, or for procedures planned prior to the patient signing the Informed Consent Form, or routine clinical procedures that are not the

result of adverse event (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered adverse events or serious adverse events. If anything untoward is reported during the procedure, that occurrence must be reported as an adverse event, either 'serious' or 'non-serious' according to the usual criteria.

In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the adverse event should be considered serious.

Disability/incapacity: an adverse event is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.

9.3 Definition of Suspected Adverse Reactions

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of Investigational New Drug safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (Guidance for Industry and Investigators [19]).

9.4 Definition of Unexpected Events/Reactions

An adverse event or suspected adverse reaction is considered ‘‘unexpected’’ if it is not listed in the Reference Safety Section of the Investigator’s Brochure (MSB11456 [2] and tocilizumab) or is not listed as the specificity or severity that has been observed; or if an Investigator’s Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator’s Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator Brochure listed only cerebral vascular accidents. ‘‘Unexpected’’ as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator’s Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation Guidance for Industry and Investigators [19].

10 ADVERSE EVENTS

10.1 Documenting Adverse Events

Participating patients will be supervised by medically qualified study investigators and designated site staff during their enrollment in this study. Study investigators are responsible for monitoring the safety of patients who have entered this study. Study investigators are responsible for all aspects of patient safety related to the study procedures. In the case of any noteworthy observation that is relevant to the benefits versus risks of the study drug or patient's safety the investigators are required to alert the Sponsor and the CRO, even if the observation may be considered an unanticipated benefit.

Patient characteristics that may signal an increased susceptibility to adverse events will be sought for at eligibility screening. Screening includes a detailed medical history, a physical examination, recording of a 12-lead electrocardiogram and a panel of laboratory tests. These measures and the responses to them serve to protect the safety of the patient when participating in this study.

Adverse events are to be recorded for the entire duration of the study in all participating patients and without consideration of the treatment group assignment.
Treatment-emergent adverse events are those that begin or increase in severity or frequency at or after the time of first treatment up to the Early Termination Visit/End of Study Visit.

At the onset of the study site staff will question each patient and will note the occurrence and nature of possible pre-existing conditions when recording the medical history. During the study, site personnel will question the patient as to any change(s) in the pre-existing condition(s), and/or the nature and details of any newly occurring or previously unresolved adverse event.

Lack of treatment effect does not qualify as an adverse event as it is the purpose of the clinical study to establish the nature and magnitude of such an effect.

10.2 Assessment of Severity

Investigators will grade all adverse events by severity using the version of NCI-CTCAE current at the time the Clinical Study Protocol was signed (unless otherwise specified). If no severity grade is proposed by the NCI, a corresponding grading is to be performed by the Investigator based on best medical judgment.

The five general levels to be used are:

- Mild (Grade 1).
- Moderate (Grade 2).
- Severe (Grade 3).
- Life-threatening (Grade 4).
- Death (Grade 5).

10.3 Assessment of Causality

Investigators are required to systematically assess the causal relationship between the adverse event and the exposure to the study drug using the following definitions:

Related:

- The adverse event follows a reasonable **temporal** sequence to study drug administration, and it cannot be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concurrent diseases, or concomitant medications).
- The adverse event follows a reasonable **temporal** sequence to study drug administration, and it is a known reaction to the drug under study or a related chemical group or is predicted by known pharmacology.

Not Related:

- The adverse event does not follow a reasonable sequence from study drug administration, or it can be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

Relevant factors for the assessment of causal relationship to the study drug include, but may not be limited to: the temporal relationship between the adverse event and the study drug, the known safety specifications of the study drug, the patient's medical history, any concomitant medication, the course of the underlying medical condition disease, or study procedures.

10.4 Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings or investigational findings (e.g., on an electrocardiogram trace) should not be reported as an adverse event unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If an abnormality fulfills these criteria, the corresponding sign, symptom or medical condition (e.g., anemia) must be reported as adverse event rather than the abnormal value (low hemoglobin) itself.

10.5 Adverse Events of Special Interest

Adverse events of special interest are untoward medical occurrences that have a special importance for the conduct of the clinical study itself and the risk management and mitigation measures put in place. These are reported on an ongoing basis and are subject to periodic review by the Medical Monitor and a Sponsor representative.

The following are considered predefined adverse events of special interest for this study:

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

Hypersensitivity is defined as an adverse event that occurs during or within 24 hours of an injection (excluding injection site reactions) that is deemed to be related to treatment. Signs and symptoms suggestive of hypersensitivity, as judged by the Investigator, will be captured and reported using the corresponding standardized Medical Dictionary for Regulatory Activities (MedDRA) queries.

Anaphylactic reactions will be diagnosed based on the Sampson criteria (Sampson, 2006 [20]) and will be analyzed using the Standard MedDRA Query: Anaphylactic reactions.

10.6 Methods of Recording and Assessing Adverse Events

At each study visit, the patient will be asked whether he or she has noticed changes in health status. Any unfavorable changes noted during the assessment period will be recorded as adverse event, whether reported by the patient, a caregiver or observed by the Investigator.

Accurate, complete and consistent information on all adverse events must be entered in a timely manner in the appropriate section of the electronic Case Report Form. All adverse events of special interest and all serious adverse events must also be documented and reported using the appropriate page in the electronic Case Report Form as described in Section 10.7 and Section 11.1, respectively.

Each record of an adverse event must include a description of the nature of the event and its duration (onset and resolution dates and times). The latter is particularly important to assess the time of onset relative to the recorded treatment administration time (time to event). In addition, the severity, its assumed causal relationship with the study drug or another aspect of the study, any supportive treatment given or other action taken (including changes in dose or regimen such as interruption or discontinuation of the study drug) and the outcome or resolution of the adverse event must be recorded. Serious adverse events must be identified and the appropriate seriousness criteria documented. Further detailed guidance can be found in the electronic Case Report Form Completion and Monitoring Conventions provided by the Sponsor.

10.7 Procedure for Reporting Adverse Events of Special Interest

In the case of a pre-specified adverse event of special interest, the Investigator must within a maximum of 24 hours after becoming aware of the event complete the Adverse Event page in the electronic Case Report Form. Adverse events of special interest must be reported to the Sponsor and CRO in the expedited manner as outlined for serious adverse event.

The Investigator may offer additional relevant documents, if available (e.g., laboratory results).

10.8 Monitoring of Patients with Adverse Events

Adverse events are monitored, recorded and assessed on an ongoing basis throughout the clinical investigation. The final outcome or resolution of adverse event is established when the patient finally ends their participation in the study (End of Study Visit) or upon completion of a Safety Follow-Up, if foreseen. All serious adverse events/adverse event of special interest ongoing at the end of the Safety Follow-Up must be monitored by the Investigator until stabilization or until the final outcome is known, unless the patient is documented as “lost to follow-up”. Reasonable attempts to the information on the final outcome must be made and documented.

After a patient’s completion of or withdrawal from the study, the Investigator remains responsible to follow as appropriate, unresolved adverse event that are serious or otherwise warrant prolonged follow-up. It is the responsibility of the Investigator to

ensure that suitable additional therapeutic measures and follow-up procedures pertaining to serious adverse event or adverse events of special interest are initiated.

10.9 Monitoring of Specific Adverse Events

Specific adverse reactions that require monitoring are described in Section 11.2. The monitoring of physical examinations (Section 7.6), vital signs (Section 7.7), imaging (Section 7.8), electrocardiogram (Section 7.9) and clinical laboratory assessments (Section 7.12) are described in their respective sections.

10.9.1 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to study drug (e.g., resulting from a drug interaction with a contraceptive medication) qualify as treatment-emergent adverse events. Nonetheless, all pregnancies with an estimated conception date during participation in this clinical investigation must be recorded by convention in the Pregnancy page of the electronic Case Report Form. This also applies to pregnancies in the female partners of male patients participating in the clinical study (see Section 10.9.2).

If any pregnancy occurs in the course of the study, then investigators or other site personnel must inform Sponsor and CRO within 1 day, i.e., immediately but no later than 24 hours of when they became aware of the pregnancy.

The Investigator must notify the Sponsor and CRO in an expedited manner of pregnancies using the Pregnancy pages of the electronic Case Report Form, which must be forwarded in the same manner as described for serious adverse event reporting (Section 11.1). Investigators must actively follow-up, document and report on the outcomes of all pregnancies.

The Investigator must notify the Sponsor and CRO of the outcomes using the Pregnancy page of the electronic Case Report Form. For abnormal pregnancy outcomes affecting the participating patient a Serious Adverse Event pages from the electronic Case Report Form are to be used. If the abnormal outcome concerns the fetus/child, Parent-Child/Fetus Adverse Event pages of the electronic Case Report Form are to be completed. Any abnormal outcome must be reported in an expedited manner as described for serious adverse event while normal outcomes must be reported within 45 days after delivery.

Should a female patient become pregnant study drug administration must be discontinued. The Sponsor or designee is to be notified without delay and the patient must be followed as mentioned above.

10.9.2 Paternal Exposure

Male patients must refrain from fathering a child or donating sperm during the study since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, has not yet been thoroughly investigated. Male patients who are sexually active must use a barrier (condom with spermicide) method of contraception and to have their female partners agree to use a highly effective contraception (i.e., methods with a failure rate of less than 1% per year as detailed in Appendix III) from the first dose until 90 days after the last dose of study drug. In the case that a partner of a male patient becomes pregnant during the study, the male patient is allowed to continue in the study.

10.9.3 Data and Safety Monitoring Committee

During the review of safety data, the Sponsor may decide to implement a Data Safety Monitoring Board to review the safety of the patients. Patient safety in this clinical investigation may be subject to further oversight by a dedicated safety committee (e.g., Data Safety Monitoring Board). In this case details concerning the committee, such as the membership and the modalities of the oversight can be found in the corresponding charter.

10.10 Definition of the Adverse Event Reporting Period

The adverse event reporting period for safety surveillance begins upon enrollment of the patient (date of first signature of first informed consent) and continues until the completion or withdrawal from the study, including any specified Safety Follow-Up.

For serious adverse events considered related to the study drug and adverse events of special interest occurring outside of the reporting period (i.e., after the end of the study), the Investigator must immediately (no later than 24 hours after becoming aware of the event) inform the Sponsor (or designee) utilizing the Safety Reporting Form.

All adverse events are to be recorded from the time the patient provided informed consent until study completion or withdrawal from the study, inclusive of Safety Follow-Up periods if foreseen. The Investigator is required to document all adverse events, whether directly observed or reported by the patient or a caregiver during open-ended, nondirected questioning. In addition, all instances of pregnancy with an onset during the study are to be recorded and reported.

11 SERIOUS ADVERSE EVENTS

11.1 Reporting Serious Adverse Events

For a new serious adverse event with an onset inside the reporting period, the Investigator must immediately (no later than 24 hours after becoming aware of the event) inform the Sponsor or its designee thereof, using the Serious Adverse Event pages from the electronic Case Report Form. This form is to be completed as outlined in the provided instructions.

In exceptional circumstances, a serious adverse event (or follow-up information) may be reported by telephone; in these cases, the Serious Adverse Event pages from the electronic Case Report Form must be completed as soon as possible.

Relevant pages from the electronic Case Report Form may supplement a serious adverse event report (e.g., medical history, concomitant medications and procedures). Additional documents may be offered by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report).

The Investigator is obliged to respond to any request for follow-up information (e.g., additional information, event outcome, final evaluation, or other records where needed) or to any question the Sponsor or designee may have concerning the serious adverse event within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited reporting obligations for events of this nature.

Requests for such follow-up information will usually be made via the designated site monitor, although a representative from Fresenius Kabi SwissBioSim Clinical Safety and Pharmacovigilance may contact the Investigator directly in exceptional circumstances to obtain further information or to discuss the event.

11.2 Reporting of Serious and Unexpected Suspected Adverse Reactions

Safety reporting has been mainly delegated by the Sponsor to the CRO. The CRO will assess reportability of each serious adverse event case version and forward a recommendation to the Sponsor for approval. The CRO will ensure that all reporting requirements according to applicable national law are followed. The CRO reports any unexpected suspected adverse reaction which occurred on the trial within the required regulatory timelines to the competent authorities. The CRO will be compliant with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs and investigators.

The Sponsor is responsible for unexpected suspected adverse reaction reporting to the regulatory authorities in the US and to Eudravigilance only. The Sponsor must report in an Investigational New Drug Safety Report any suspected adverse reaction to study drug (i.e., including active comparators) that is both serious and unexpected.

Before submitting an Investigational New Drug Safety Report, the Sponsor needs to ensure that the event meets all three of the definitions (Guidance for Industry and Investigators [19]):

- Suspected adverse reaction.
- Serious.
- Unexpected.

If the adverse event does not meet all three of the definitions, it should not be submitted as an Investigational New Drug Safety Report.

The timeframe for submitting an Investigational New Drug Safety Report, any serious unexpected suspected adverse reaction which is not fatal or life-threatening to the FDA is no later than 15 calendar days after the Sponsor determines that the suspected adverse reaction or other information qualifies for reporting.

Unexpected fatal or life-threatening suspected adverse reactions shall be reported by the Sponsor to the FDA no later than 7 calendar days after the Sponsor's initial receipt of the information (in accordance with 21 CFR 312.32(c)(2)).

The day of initial receipt for cases that are interpretable as single cases and the day the Sponsor determines that multiple cases qualify for expedited reporting are considered day zero.

If FDA requests any additional data or information, the Sponsor shall submit it to the FDA as soon as possible, but no later than 15 calendar days after receiving the request (in accordance with 21 CFR 312.32(c)(1)(v)).

The CRO is responsible for unexpected suspected adverse reaction reporting to the regulatory authorities.

The CRO will prepare submissions and submit to regulatory agencies by email, fax, courier, local country officer, or hand-carried submission as required by country or local regulations. The Sponsor will perform electronic submissions to E2B to the European Medicines Agency (EMA) and the CRO to competent authorities in the European Economic Area as required by country or local regulations.

The CRO is responsible for unexpected suspected adverse reaction reporting to ethics committees according to local legislation. The CRO will distribute safety letters to central ethics committees and IRBs as required by country or local regulations.

The CRO will ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the Ethics Committee and in any case no later than 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional 8 days.

All other suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by [redacted] (in accordance with Article 17(1)(a), (b) and (d) of European Directive 2001/20/EC).

The CRO is responsible for unexpected suspected adverse reaction reporting to the investigators according to local. The CRO will distribute safety letters to sites as required by country or local regulations.

11.2.1 Overdose

An overdose is defined as any dose greater than the highest daily dose included in a Clinical Study Protocol. An overdose may also include cases where the highest daily dose is not exceeded but the frequency of dosing is not adhered to as stipulated by the Clinical Study Protocol. Each case when two doses are not separated by at least 5 days should be handled as an overdose. In the event of an overdose, patients should receive appropriate supportive medical care and be followed until resolution/stabilization of any clinical issues.

Even if it does not meet other criteria for a serious adverse event, any instance of overdose (suspected or confirmed and irrespective of whether or not it involved MSB11456 or EU-approved RoActemra) must be recorded in the study medication section of the electronic Case Report Form and reported to Fresenius Kabi SwissBioSim GmbH or a specified designee in an expedited manner within 24 hours of awareness. Details of any signs or symptoms and their management should be fully recorded including details of any antidote(s) administered.

In the event of a suspected overdose of study drug, the Investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the patient for any adverse events/serious adverse events and laboratory abnormalities for at least five half-lives of study drug.
- Document the quantity of excess dose as well as the duration of the overdose in the electronic Case Report Form.
- Decisions regarding dose interruptions/modifications/discontinuations will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.
- The administration of the study drug in the cases of suspected overdose will be suspended until a decision is made by the Investigator in consultation with the Medical Monitor.
- The Investigator will use their clinical judgment to treat any overdose.

Overdose does not automatically make an adverse event serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as a serious adverse event (see Section 11.1).

For overdoses associated with a serious adverse event, the standard serious adverse event reporting timelines apply (i.e., 24 hours, see Section 11.1).

Overdoses will be reported in the Serious Adverse Event Form whether they are non-serious or serious events. The serious adverse event criterion medically significant event is to be selected for overdoses that have been reported as serious adverse events.

11.3 Safety Reporting to Regulatory Oversight

Certain observations made during a clinical investigation may require notification to Health Authorities and/or IEC/IRB. The CRO will send appropriate safety notifications to these oversight bodies in accordance with applicable laws and regulations. To support compliance with these requirements the Investigator must provide requested information in a timely manner.

In accordance with International Council on Harmonisation (ICH) GCP, the CRO will inform investigators of "findings that could adversely affect the safety of patients, impact the conduct of the study and/or alter the favorable opinion of the IEC/IRB to continue the trial." In line with applicable regulations, the CRO will inform the Investigator of any

adverse event categorized as serious and unexpected and considered related to the study drug ("suspected unexpected serious adverse reactions"). The Investigator should place copies of any received Safety Reports in the Investigator Site File, as well as fulfilling additional national regulations concerning Safety Report notifications, as applicable.

Where required by regulations, the CRO will send appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the CRO and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the CRO will report serious adverse events/suspected unexpected serious adverse reactions/safety in accordance with that Directive and with the related detailed guidance documents.

12 STATISTICS

12.1 General Procedures

Full details of all planned analyses will be provided in the Statistical Analysis Plan, to be finalized and approved prior to the database lock for the Week 30 CSR.

The following descriptive statistics will be used to summarize the study data per treatment group on the basis of their nature unless otherwise specified:

- Continuous variables: Number of non-missing and missing observations, mean, standard deviation, median, minimum and maximum.
- Categorical variables: Frequencies and percentages.

If not otherwise specified:

- Data collected before and analyzed at the end of the Core Treatment Period (Day 1 to Day 169/Week 24) will be summarized per initial treatment group.
- Data collected or analyzed after the re-randomization will be summarized for the following three treatment groups: MSB11456 during the complete study duration, EU-approved RoActemra during the complete study duration, switch from EU-approved RoActemra to MSB11456.

The primary variable will be analyzed in the context of a therapeutic equivalence study. Treatment differences and 95% confidence interval (for the EMA) or 90% confidence interval (for the FDA) will be provided for the primary endpoint.

12.2 Sample Size

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

For the FDA:

A total of 460 evaluable patients (230 per arm) will provide 90% power to demonstrate equivalence between treatments for the primary endpoint, with equivalence margins of [-0.6, 0.5] and a type I error of 5%, assuming no difference between the two treatment groups and a common standard deviation of 1.76 (derived from Genovese, 2008 [21]; Smolen, 2008 [22]; Kremer, 2011 [23]).

For the EMA:

A total of 460 evaluable patients (230 per arm) will provide 90% power to demonstrate equivalence between treatments for the primary endpoint, with equivalence margins of ±0.6 and a type I error of 2.5%, assuming no difference between the two treatment groups and a common standard deviation of 1.76.

In addition, this sample size provides more than 80% power to demonstrate that the 95% confidence interval for the difference between treatments in the secondary efficacy endpoint ACR20 response rate at Week 24 will be included in the equivalence interval [-15%, +15%], assuming no difference between the two treatment groups and that both MSB11456 and tocilizumab have an ACR20 response rate of 60% at Week 24 (Genovese, 2008 [21]; Smolen, 2008 [22]; Kremer, 2011 [23]).

The drop-out/protocol deviation rate will be monitored on blinded data throughout the first 24 weeks. If larger than anticipated (>15%), an investigation on the reasons for dropping out will be conducted. The number of randomized patients may be adjusted as a consequence.

The sample size for the population pharmacokinetic sub-study will be a subset of approximately 30 patients per group, for a total of 60 patients (to ensure that approximately 50 patients complete the pharmacokinetic sub-study).

12.3 Randomization

Randomization will be performed via a centralized IRT system. Eligible patients will be randomly assigned to either MSB11456 or EU-approved RoActemra in a 1:1 ratio, stratified by previous exposure to biological treatment for rheumatoid arthritis (yes/no) which is a prognostic factor.

Patients with previous exposure to any biologic treatment will be capped at 10% of the total study population.

Randomization will be conducted in permuted blocks.

At the Week 24 Visit, patients who were initially randomized to the EU-approved RoActemra group will be re-randomized in a 1:1 ratio to receive either 162 mg MSB11456 or EU-approved RoActemra at the Week 24 Visit and weekly thereafter until Week 51. Patients who were initially randomized to the MSB11456 group will remain on 162 mg weekly treatment with MSB11456 throughout the entire study. Patients who discontinue study drug before or at Week 24 will not be re-randomized at Week 24 and will discontinue the study.

12.4 Analysis Sets

For the purposes of the analysis, the following analysis sets are defined in Table 5.

Table 5 Study Analysis Sets

Analysis Set	Description
Intent-To-Treat	The Intent-To-Treat Analysis Set includes all randomized patients. Patients will be analyzed according to their randomized treatment. The Intent-To-Treat Analysis Set will be the primary analysis set for efficacy and will be used for all primary, secondary and other efficacy endpoint analyses.
Per Protocol	The Per Protocol Analysis Set includes all randomized and treated patients (hence a subgroup of the Intent-To-Treat Analysis Set) who do not have any clinically important protocol deviations before the primary efficacy endpoint analysis time point (Week 24), with respect to factors likely to affect the efficacy of treatment. Patients will be analyzed according to their randomized and received treatment, as receipt of a different treatment from that assigned is a clinically important protocol deviation. The Per Protocol Analysis Set will be used for the primary, secondary and other endpoint analyses.
Safety	The Safety Analysis Set will include all patients who receive at least one dose of study drug (MBS11456 or EU-approved RoActemra). Patients will be analyzed according to the actual treatment they receive. The Safety Analysis Set will be used for all secondary and other safety, and immunogenicity endpoints analyses.
Pharmacokinetic	All patients who have at least one measurement of trough concentration and without important protocol deviations impacting pharmacokinetics.

12.5 Statistical Methods

12.5.1 Primary Efficacy Analyses

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 [3]).

In order to be in line with both EMA and FDA requirements, different acceptance margins are predefined for the primary endpoint mean absolute change from baseline in DAS28-ESR at Week 24.

Equivalence margins of ±0.6, correspond to the retention of approximately 65% of conservative estimates of treatment effect sizes relative to placebo for tocilizumab, based on the upper bound of 95% confidence interval from a meta-analysis performed by the Sponsor (The meta-analysis was performed using the following publications Genovese, 2008 [21]; Smolen, 2008 [22]; Kremer, 2011 [23]; Emery, 2008 [24]).

- For the FDA, the equivalence 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 19 October 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 RoActemra.

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

Change from baseline at Week 24 in DAS28-ESR will be analyzed using an analysis of covariance with study drug, and previous exposure to biologic treatment for rheumatoid arthritis (yes/no) strata as fixed effects and baseline DAS28-ESR as a covariate. The difference between treatments will be estimated by the least squares mean difference between MSB11456 and tocilizumab, with its 95% confidence interval for the EMA and its 90% confidence interval for the FDA.

- For the FDA: MSB11456 will be considered equivalent to tocilizumab if the 90% confidence interval for the difference in mean change from baseline to Week 24 in DAS28-ESR between MSB11456 and tocilizumab lies entirely within the equivalence interval of [-0.6, 0.5] in the Intent-To-Treat Analysis Set.

- For the EMA: MSB11456 will be considered equivalent to tocilizumab if the 95% confidence interval for the difference in mean change from baseline to Week 24 in DAS28-ESR between MSB11456 and tocilizumab lies entirely within the equivalence interval of [-0.6, 0.6] in the Intent-To-Treat Analysis Set.

Patients who discontinue treatment before Week 24 (Core Treatment Period) will be asked to return for all planned assessments visits of the Core Treatment Period. All available values will be used in the analysis, including the DAS28-ESR values of patients who discontinued treatment before Week 24 Visit, but completed Week 24 Visit efficacy assessments (as requested in the study). For missing values of DAS28-ESR at Week 24, details of the data handling will be provided in the Statistical Analysis Plan.

12.5.2 Secondary and Other Endpoint Analyses

All secondary and other endpoints are specified in Section 3.2 and Section 3.3, respectively.

All secondary and other efficacy endpoints will be analyzed on the Intent-To-Treat and Per-Protocol Analysis Sets. All secondary and other safety, and immunogenicity endpoints will be analyzed on the Safety Analysis Set. The primary efficacy analysis will also be performed on the Per Protocol Analysis Set.

The response rates will be compared using 95% stratified (on previous exposure to biologic treatment) Newcombe confidence intervals for the difference. For the analysis of longitudinal continuous data, mixed-effect repeated measure models will be employed. The fixed effects of treatment, visit, treatment-by-visit-interaction and stratification factors will be included in the model and the 95% confidence interval for the least-squared mean at each time point will be provided.

For time to event variables, results will be summarized by means of Kaplan-Meier curves together with a summary of associated statistics (median, confidence interval) and the number of patients at risk.

Descriptive summary statistics will be given throughout.

Specificities of Secondary Efficacy Endpoint "ACR20 at Week 24"

The treatment difference in ACR20 at Week 24 will be assessed versus predefined margins. The equivalence margins are set to ±15%. These proposed equivalence margins correspond to 50% retention of conservative estimates of the effect size of tocilizumab relative to placebo (derived from Genovese, 2008 [21]; Smolen, 2008 [22]; Kremer, 2011 [23]; Emery, 2008 [24]) using meta-analysis).

12.5.3 Sensitivity Analyses

Sensitivity analyses for the primary endpoint and secondary endpoints based on different missing data mechanism assumptions may be explored and will be pre-specified in detail in the Statistical Analysis Plan which will be ready and approved before the Week 30 partial database lock and unblinding.

12.5.4 Patient Disposition

The following information will be summarized for patient disposition:

- Number of patients randomized at the initial and second randomizations will be tabulated by country, and center.
- Patient disposition at Week 24 and at the end of the study (Week 52) (including the number of patients who were randomized, treated with study drug, completed treatment, discontinued treatment with reason for discontinuation, completed study, and discontinued study with reason for discontinuation).
- Summaries of analysis sets with reason for exclusion.
- Important protocol deviations leading to exclusion from the Per Protocol and/or Pharmacokinetic Analysis Sets.
- Randomization list of patients and their actual versus randomized treatment group and strata.

12.5.5 Demographic and Baseline Characteristics

If permitted by local regulation, the following demographic data will be summarized: age (in years, at time of signing informed consent), race, sex, ethnicity, height, weight and body mass index.

The last value before treatment start will be considered for these summaries.

Further data that was only collected at screening (e.g., follicle-stimulating hormone test, serum pregnancy test) will be displayed in data listings.

12.5.6 Medical History

Rheumatoid arthritis disease phenotype and duration as well as time from first diagnosis, and previous treatments administered for rheumatoid arthritis (including previous use of biologic or non-biologic therapy for rheumatoid arthritis) will be summarized by descriptive statistics.

Information on history of tuberculosis or any treatment for active/latent tuberculosis, previous surgeries and smoking status will be listed.

Other medical history will be coded according to the latest version of MedDRA and will be summarized by system organ class and preferred term by initial treatment group and overall.

12.5.7 Chest X-Ray

Chest X-ray data collected at the Screening Visit, the Safety Follow-Up Visit at Week 55 and End of Study Visit at Week 63 will be listed.

12.5.8 Study Drug Administration

For the study drug, summary statistics will be provided for the total number of doses and total duration of exposure throughout the Core Treatment Period and the Extended Treatment Period.

In addition, compliance will be estimated as the proportion of the planned number of injections actually administered. Compliance will be summarized up to Week 24 (Core Treatment Period) and up to Week 52 (Extended Treatment Period) as a continuous variable, as well as the number and percent of patients with ≤80%, >80% to ≤100% and >100% compliance.

12.5.9 Safety Analyses

If not specified otherwise, safety endpoints will be summarized up to Week 24 (Core Treatment Period), Week 30, Safety Follow-Up Visit at Week 55 and End of Study Visit at Week 63 by treatment group using the Safety Analysis Set.

12.5.9.1 Adverse Events

Adverse events will be coded according to the latest version of MedDRA and will be summarized by treatment group overall, by severity and by relationship to MSB11456 or EU-approved RoActemra.

Treatment-emergent adverse events, i.e., adverse events that started or worsened during the treatment period, will be summarized by presenting the number and percentage of patients and the number of events in each system organ class and preferred term.

The subsets of adverse events suspected of a relationship to study drug, serious adverse events, serious adverse events suspected of a relationship to study drug, adverse events leading to premature discontinuation of the treatment and adverse events of special interest will be presented similarly.

12.5.9.2 Injection Site Reactions

Injection site reactions will be summarized by treatment group.

12.5.9.3 Vital Signs and Physical Examinations

Vital sign data (observed values and changes from baseline) will be summarized using descriptive statistics by time point and treatment.

The number of patients with vital signs outside the normal ranges will be summarized by time point and treatment group.

Abnormalities in physical examination will be listed.

12.5.9.4 Clinical Laboratory Values

Clinical laboratory values comprise clinical chemistry and hematology, lipid panel and urinalysis assessments.

Summary statistics will be used to present observed values and changes from baseline in continuous laboratory variables.

Shift tables will be used to present changes in categorical laboratory variables.

Where applicable, hematology and clinical chemistry laboratory results will be graded using the latest version of the NCI-CTCAE criteria. These laboratory NCI-CTCAE toxicity grades will also be summarized by visit and shift from baseline to worst on treatment NCI-CTCAE toxicity grade.

Patient listings and summary statistics at each assessment time will be presented using the International System of Units.

Clinically significant abnormal values will be displayed in a listing. This listing will additionally present the rest of the respective patient's values for the questionable laboratory parameter in order to display the conspicuous values in a chronological context.

12.5.9.5 12-Lead Electrocardiogram

Shift tables of clinically significant 12-lead electrocardiogram abnormalities will be provided.

12.5.10 Immunogenicity Analyses

Immunogenicity endpoints will be analyzed descriptively for the Safety Analysis Set. The proportion of patients testing positive for antidrug antibodies, their titer and the proportion of patients with neutralizing antidrug antibodies will be presented by treatment group and by scheduled visit and overall.

12.5.11 Pharmacokinetic Analyses

Serum trough concentrations of tocilizumab will be listed and summarized by treatment and time point of collection. Summary statistics in the tabulation will include n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and geometric coefficient of variation.

The pharmacokinetic analyses will be performed on the Pharmacokinetic Analysis Set. The details of the population pharmacokinetic analysis will be described in a Pharmacokinetic Analysis Plan and the results will be reported in a separate report.

12.5.12 Concomitant Medications and Procedures

Concomitant medications and procedures will be coded using the World Health Organization Drug Dictionary and will be summarized up to Week 24 (Core Treatment Period), Week 52 (Extended Treatment Period) and the End of Study Visit at Week 63 by treatment group giving the number and percentage of patients by medication and medication category.

12.5.13 Further Data

Further data collected (e.g., serology, urine pregnancy test, rheumatoid factor, anti-cyclic citrullinated protein antibodies, anti-nuclear antibodies, anti-double-stranded DNA, QuantiFERON®-TB Gold Plus Test) will be displayed in listings.

12.5.14 Missing Data and Intercurrent Events

Details on the handling of missing data and intercurrent events will be provided in the Statistical Analysis Plan.

12.6 Reporting Time Points

There will be three main analysis points in the study:

- The primary efficacy analysis at Week 24 will be conducted after all patients have completed the Week 30 assessments, or have terminated the study before Week 30. The descriptive summaries in this report will include all data up to and including data from the Week 30 Visit. Outputs which include data from the Extended Treatment Period (Weeks 24 to 30) will have an additional treatment group to account for the patients who switched treatment from EU-approved RoActemra to MSB11456 at Week 24.

- The full clinical study analysis will be conducted at Week 55 after all patients have completed the Week 52 (Extended Treatment Period) and the Safety Follow-Up assessments, or have terminated the study before Week 52.

- The final analysis will include the End of Study assessments at Week 63 and will be reported in a CSR Addendum.

The population pharmacokinetic sub-study results will be reported separately.

Primary and secondary efficacy, safety, and immunogenicity objectives will be assessed up to Week 24 (Core Treatment Period). This primary analysis will be performed when all the patients have reached Week 30 (partial database lock). Results of the Week 24 and Week 30 analyses will be included in the same CSR after Week 30 partial database lock. This CSR will be called the "Week 30 CSR." As the study remains blinded until the final database lock an independent team at the CRO is required to perform and process these analyses. Details on who will be unblinded in the context of the Week 30 CSR will be given in a Data Access Plan to be finalized before the Week 30 unblinding will be performed. However, the Sponsor will be unblinded at the time of the Week 30 results.

The "Week 55 CSR" will contain the Week 55 analysis, including all time points up to Week 52 as well as the Safety Follow-Up Visit 4-weeks after the end of treatment (partial database lock). The Week 55 CSR will include all analyses and descriptive summaries produced for the Week 30 CSR, in addition to descriptive summaries for all data collected after Week 30.

A Safety Follow-Up CSR Addendum will be prepared with the 3-month Safety Evaluation data (Week 63; final database lock).

13 DATA MANAGEMENT

13.1 Data Collection

Clinical data will be entered into Medidata Rave Electronic Data Capture system provided by the CRO.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

The Investigator is responsible for ensuring accuracy, completeness, legibility, and timeliness of the data reported and must certify that the data entered in the electronic Case Report Form are complete and accurate.

The Investigator must maintain source documents for each patient in the study. All information in the electronic Case Report Form must be traceable to these source documents.

Blood samples for the pharmacokinetic analyses will be sent to the designated bioanalytical laboratory for processing and the results be sent electronically to the CRO, preferably in study data tabulation model, when possible.

13.2 Data Management and Quality Control

The Electronic Data Capture system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

In addition, CRO staff will review the data entered into the electronic Case Report Form for completeness and accuracy. Request for data clarification will be sent to the investigational site using electronic data query. Designated investigator site staff are required to respond to the query and confirm or correct the data.

The data collected by vendors will be electronically transferred to the CRO through datasets. Consistency of these data with the data recorded in the electronic Case Report Form will be reconciled by the CRO. Request for clarification of data will be sent to the investigational site or bioanalytical laboratory (or third vendor), as appropriate. All data discrepancies will be resolved prior to database lock.

Concomitant medications entered into the database will be coded using the most current World Health Organization Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug

therapies, medical history and adverse events will be code using the most current MedDRA terminology.

13.3 Record Retention

After database lock, the Investigator will receive electronic copies of the patient data for archiving at the investigational site.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years has elapsed since the formal discontinuation of clinical development of the study intervention, but at least for 25 years after the end of the clinical trial in line with the requirements set by EU Regulation 536/2014. However, the medical files of patients shall be archived in accordance with national law but at least for 5 years after study completion as stipulated by EU regulation 536/2014 and EU Directive 2005/28/EC. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without with written consent of the Sponsor, if applicable. It is responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

14 ETHICS AND RESPONSIBILITIES

14.1 Ethics Committee

This study will be conducted in compliance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, in compliance with ICH GCP E6(R2) Guidelines and according to the appropriate regulatory requirements in the countries where the study will be conducted, e.g., Title 21 of the United States Code of Federal Regulations, EU Directives 2001/20/EC, EU Directive 2005/28/EC and EU Regulation 536/2014.

In addition, this study will adhere to all local regulatory requirements and requirements for data protection.

The conduct of the study is conditioned by an appropriately constituted IRB/IEC approval.

Before initiating a study and enrolling any subject/patient, the Investigator/institution must have written and dated approval/favorable opinion from the IRB/IEC for the Clinical Study Protocol/amendment(s), Informed Consent Form) and subsequent consent form updates, subject/patient recruitment materials (e.g., advertisements), Investigational Brochure, and any written information to be provided to subject/patients.

The Investigator must obtain a statement from the IRB/IEC that they comply with GCP requirements. The IRB/IEC approval must identify the protocol version as well as the documents reviewed.

If required by local regulations, the study should be re-approved by the IEC annually

14.2 Good Clinical Practice

This study will be conducted in compliance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, in compliance with ICH GCP E6(R2) Guidelines and according to the appropriate regulatory requirements in the countries where the study will be conducted, e.g., Title 21 of the United States Code of Federal Regulations, EU Directives 2001/20/EC, EU Directive 2005/28/EC and EU Regulation 536/2014.

In addition, this study will adhere to all local regulatory requirements and requirements for data protection.

As per regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on Clinical Trials on Medicinal Products for Human use, and repealing

Directive 2001/20/EU, Article 52, a 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

Fresenius Kabi SwissBioSim GmbH will identify, investigate and report Serious Breach as required by applicable regulation

Fresenius Kabi SwissBioSim GmbH who is the Sponsor of a clinical trial shall notify in writing the relevant regulatory authority of any serious breach identified during the course of the study within 7 days of becoming aware of that breach.

During a clinical trial, when Fresenius Kabi SwissBioSim GmbH may become aware of serious breaches of the rules for the conduct of that clinical trial, Fresenius Kabi SwissBioSim GmbH will report to the Member States concerned in order for action to be taken by those Member States, where necessary.

14.3 Patient Data Protection

All information, including personal data, relating to individuals (data patients) will be treated as confidential by the Investigator and staff at the CRO, and the CRO warrants that processing of personal data will be in compliance with the EU General Data Protection Regulation and all applicable data protection law [25].

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

14.4 Informed Consent

An unconditional prerequisite for a subject's participation in the study is his/her written informed consent which must be given before any study-related activities are carried out in compliance with ICH GCP requirements.

All subjects will be informed in writing regarding the objectives, procedures and risks of study participation. The subjects will sign the Informed Consent Form that contains information about the objectives of the study, the procedures followed during the study, and the risks and restrictions of the study, with special reference to possible side effects of the medication and potential interactions.

In addition to providing this written information to a potential subject, the Investigator or designee will inform the subject verbally of all pertinent aspects of the study. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons. The Informed Consent Form must be signed and personally

dated by the subject and the Investigator (or sub-investigator[s] to whom this was delegated). Note: A separate Informed Consent Form (containing important information about COVID-19, clinical research study participation and patient consent) will be provided to and signed by each patient to provide information on the general risks of study participation related to COVID-19 and to document that it is understood by the patient. Another separate Informed Consent Form will be required to be understood and signed by partners of male participating patients who become pregnant during the study or within 10 weeks after the participating patient's last dose of study drug.

Both the subject and the Investigator will sign an original copy of the Informed Consent Form. A copy of the signed and dated Informed Consent Form will remain at the Investigator's site and must be safely archived by the Investigator so that it can be retrieved at any time for monitoring, auditing, and inspection purposes. Another copy of the signed and dated Informed Consent Form should be provided to the subject prior to participation. Whenever important new information that may be relevant to the subject's consent becomes available, the written Informed Consent Form and any other written information provided to subjects will be revised by Fresenius Kabi SwissBioSim GmbH or designee and be submitted again to the IRB/IEC for review and favorable opinion. The agreed, revised information will be provided to each patient in the study for signing and dating. The Investigator or designee will explain the changes from the previous version to all subjects in the study prior to reconsent."

14.5 Source Documentation

The Investigator or designee will record data, derived from the source documents, into the electronic Case Report Form, after having received training both on the Electronic Data Capture system and electronic Case Report Forms. The Investigator should complete and maintain all source documents in accordance with the ALCOAC principles (Attributable, Legible, Contemporaneous, Original, Accurate and Complete) in compliance with ICH GCP E6 R2.

14.6 Study Files

The Investigator shall take responsibility for maintaining adequate and accurate source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor, its representatives and regulatory authorities. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.

14.7 Financing and Insurance

14.7.1 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a Clinical Study Agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory and other protocol-required services are being paid directly or indirectly.

14.7.2 Insurance, Indemnity, and Compensation

The Sponsor will maintain an appropriate clinical study insurance policy.

14.7.3 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

15 AUDITING AND MONITORING

15.1 Audits and Inspections

Representatives from regulatory authorities, IRB/IEC, Fresenius Kabi SwissBioSim GmbH's and/or CRO Clinical Quality Assurance may request access to all source documents, electronic Case Report Forms and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times during these activities.

Authorized representatives of the Sponsor Fresenius Kabi SwissBioSim GmbH/CRO, a regulatory authority, or an IRB/IEC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, current ICH guidelines and any applicable regulatory requirements.

15.2 Monitoring of the Study

The CRO will perform the monitoring of the study according to CRO's monitoring plan and applicable Standard Operating Procedures to review that the study is conducted and documented properly in compliance with the protocol, ICH GCP, and all applicable regulatory requirements.

During the study, a CRO representative will have regular contacts with the study site, including remote and on-site visits to:

- Provide study information and support to the Investigator(s).
- Confirm that facilities remain fit for purpose and that the site has appropriate resources available to conduct the study in compliance with the Clinical Study Protocol and are able to collaborate with the CRO monitoring team.
- Confirm that the investigational team is adhering to the Clinical Study Protocol requirements, that data are being accurately and timely recorded in the electronic Case Report Form, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed.
- Perform direct source data verification as defined in the Clinical Monitoring Plan by comparing electronic Case Report Form data with the patient's source document at the investigational site including verification of informed consent of participating patient.

- Discuss with the Investigator any deviation from the Clinical Study Protocol and other study instruction, and review that there are timely and completely reported accordingly.

- Review with the Investigator any safety events for timely and complete reporting.

- Work closely with the Investigator and site staff to facilitate effective management of the study in compliance with the Clinical Study Protocol, ICH GCP Guidelines and applicable regulatory requirements.

- The CRO representative will be available between visits if the Investigator(s) or other staff at the center needs information and advice about the study conduct.

15.3 Study Agreements

The Principal Investigator at each/the center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between Fresenius Kabi SwissBioSim GmbH and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

15.4 Deviation from the Clinical Study Protocol

The Investigator(s) must not deviate from or make any changes to the Clinical Study Protocol without documented agreement between the Principal Investigator and Fresenius Kabi SwissBioSim GmbH or the IRB approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the patients or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical study (e.g., changes to the organization/structure of the Fresenius Kabi SwissBioSim GmbH, the name/department name of the study site, the address or phone number of the study site or Fresenius Kabi SwissBioSim GmbH, the job title of the Investigator and monitors).

The Investigator(s) should document any deviation from the Clinical Study Protocol regardless of their reasons. Only when the Clinical Study Protocol was not followed in order to avoid an immediate hazard to the patients or for other medically compelling reason, the Investigator should prepare and submit the records explaining the reasons

thereof to Fresenius Kabi SwissBioSim GmbH and the head of study site and retain a copy of the records.

The Sponsor and the CRO will identify and review risks as specified in the Clinical Monitoring Plan.

15.5 Study Timetable and End of Study

The end of the study is defined as the last patient's last visit.

The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. Fresenius Kabi SwissBioSim GmbH may also terminate the entire study prematurely if concerns for safety arise within this study or any other study with the study drug.

15.6 Protocol Amendments

In accordance with ICH GCP E6(R2) Guideline, the Investigator should not implement any deviation from or changes to the protocol without agreement by the Sponsor and prior review and documented approval from the IRB/IECs of a protocol amendment, except where necessary to eliminate an immediate hazard(s) to study patients, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor[s], change of telephone number[s]).

Any change to the protocol must be handled as a protocol amendment. Any potential amendment must be approved by the Sponsor. A written amendment must be submitted to the appropriate regulatory authorities and to the IRB/IECs assuming this responsibility. The Investigator must await IRB/IEC approval of protocol amendments before implementing the changes, except where necessary to eliminate apparent immediate hazard to patients.

Per ICH GCP E6R2 4.5.4 the Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

- To the IRB/IEC for review and approval/favorable opinion.
- To the Sponsor for agreement and, if required.
- To the regulatory authority(ies).

All amendments to the protocol must be approved in writing by both the appropriate regulatory authorities and the IRB/IEC, except for administrative amendments, which require notification but not written approval. Once approved, the protocol amendment will be distributed to all recipients of the original protocol, with instructions to implement the amendment to the protocol.

If, in the judgment of the local IRB/IEC, the Investigator and/or Sponsor, the protocol amendment alters the study design, procedures and/or increases the potential risk to the patient, the currently approved written Informed Consent Form will require modification. The modified Informed Consent Form must also be reviewed and approved by the Sponsor, appropriate regulatory authorities, and the IRB/IEC. Whenever applicable repeat informed consent should be obtained from patients enrolled in the study before participation continues.

16 STUDY REPORT AND PUBLICATIONS

As described in Section 12.6, two CSRs will be prepared: Week 30 CSR will contain the results of the Week 24 and Week 30 (partial database lock) analyses and a Week 55 CSR contain the Week 55 analysis, including all time points up to Week 52 as well as the Safety Follow-Up Visit 4 weeks after the end of treatment (partial database lock). The Week 55 CSR will include all analyses and descriptive summaries produced for the Week 30 CSR, in addition to descriptive summaries for all data collected after Week 30.

A Safety Evaluation CSR Addendum will be prepared with the 3-month Safety Evaluation data (Week 63; final database lock).

The publication policy of Fresenius Kabi SwissBioSim GmbH is discussed in the Investigator's Clinical Research Agreement.

The posting of Fresenius Kabi SwissBioSim GmbH sponsored study information and tabular study results on the respective public registry and as required any national accessible websites will be done by the CRO.

17 STUDY DISCONTINUATION

The Sponsor may discontinue the study if it becomes unjustifiable for medical or ethical reasons, for poor enrolment, or because of discontinuation of clinical development of MSB11456 or withdrawal of Actemra/RoActemra from the market.

Health Authorities and IECs/IRBs will be informed about the discontinuation of the study in accordance with applicable regulations.

18 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Fresenius Kabi SwissBioSim GmbH. However, authorized regulatory officials, IRB/IEC personnel, Fresenius Kabi SwissBioSim GmbH and its authorized representatives are allowed full access to the records [25].

19 REFERENCES

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