IB	Investigator's Brochure
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention To Treat
IWRS	Interactive Web Response System
JIA	Juvenile Idiopathic Arthritis
LS	Least Squares
LTBI	Latent TB Infection
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
PD	Pharmacodynamics
PK	Pharmacokinetics
PRO	Patient-Reported Outcome
QFT	QuantiFERON-TB Gold test
QoL	Quality of Life
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
s.c.	Subcutaneous
SDAI	Simplified Disease Activity Index
SF-36	36-item Short Form Health Survey
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TNF	Tumor Necrosis Factor
US	United States
VAS	Visual Analog Scale

Objectives:

Primary Objective

The primary objective of this study is to evaluate the safety profile of MSB11022-CCI compared to Humira® in patients with moderately to severely active rheumatoid arthritis (RA) up to Week 52.

Secondary Objectives

The key secondary objective is to compare the efficacy of MSB11022-CCI to Humira® at Week 12 in patients with moderately to severely active RA.

Other secondary objectives include:

- To evaluate the immunogenicity profile of MSB11022-CCI compared to Humira® in patients with moderately to severely active RA up to Week 52
- To further compare the efficacy and safety of MSB11022-CCI compared to Humira® in patients with moderately to severely active RA up to Week 52
- To compare quality of life (QoL) and physical function on MSB11022-CCI with Humira® in patients with moderately to severely active RA
- To compare injection site pain levels of MSB11022-CCI versus Humira®

Exploratory Objective

The exploratory objective is to evaluate population pharmacokinetics (PK) on MSB11022-CCI and Humira® in patients with moderately to severely active RA.

Methodology: This trial is a two-arm, randomized, multicenter, double-blind, parallel group trial designed to compare the safety, immunogenicity, and efficacy of MSB11022-CCI with Humira® in approximately 260 randomized patients with moderately to severely active RA during a 52 week period.

Baseline is defined as the day on which the first dose of the investigational medicinal product (IMP) (blinded trial drug) is administered (Week 0). The trial will include a pre-trial evaluation period (screening period, from 28 days to 3 days prior to drug administration), a double-blind 48-week treatment period to evaluate long-term safety and immunogenicity, a 4-week safety follow-up visit, and a 4-month safety evaluation period. The primary safety endpoint will be assessed up to Week 52, key secondary efficacy endpoint will be assessed at Week 12. The analysis for the key secondary efficacy endpoint will be descriptive.

Re-screening will be allowed once for those patients who do not meet the inclusion/exclusion criteria within the above specified time limits. The Medical Monitor must promptly inform the Sponsor about requests and reasons for re-screening. An Independent Data Monitoring Committee (IDMC) will review the safety data from this trial on an ongoing basis.

Eligible patients will be randomized in permuted blocks in a 1:1 ratio by an interactive web response system (IWRS) to receive either MSB11022-CCI subcutaneous (s.c.) or Humira® s.c. at a dose of 40 mg every other week starting at baseline up to and including Week 48.

Day/Week	Screening	Day 1 Week 0 (Baseline)	W2	W4	W6	W8	W12	W24[a]	W36	W48	W52[b]	ET[b]	4-week safety FU (4 weeks after last dose of IMP)[c]	4-month safety evaluation (4 months after last dose of IMP)[c]
Visit window (days)	-28 days to -3 days	None	± 2	± 2		± 2	± 2	± 2	± 2	± 2	± 2	± 7	± 7	± 7
Viral serology[l]	X													
Tuberculosis Quantiferon-Gold test[m]	X							X[m]			X[m]	X[m]		
Chest X-ray[n]	X													
12-lead ECG[o]	X						X	X			X	X		
Patient's Global Assessment of Disease Activity[p]	X	X	X	X		X	X	X			X	X		
Physician's Global Assessment of Disease Activity[p]	X	X	X	X		X	X	X			X	X		
Patient assessment of arthritis pain[p]	X	X	X	X		X	X	X			X	X		
HAQ-DI[p]	X	X	X	X		X	X	X			X	X		
Tender joint count	X	X	X	X		X	X	X			X	X		
Swollen joint count	X	X	X	X		X	X	X			X	X		
C-Reactive protein	X	X	X	X		X	X	X			X	X		
Erythrocyte sedimentation rate[q]	X	X	X	X		X	X	X			X	X		
Sampling for immunogenicity[r]	X[s]	X	X	X			X	X	X		X	X		
PK sample[r]		X	X	X			X	X	X		X	X		
Injection site pain (VAS)[t]				X	X[u]	X								
Adverse events, concomitant medications and procedures	X	X	X	X		X	X	X	X	X	X	X	X	X

2 Sponsor, Investigators and Trial Administrative Structure

The Sponsor of this clinical trial with MSB11022 is EMD Serono Research & Development Institute, Inc. (EMD Serono R&D), Billerica, MA, in the United States of America (USA) and Merck KGaA, Darmstadt, Germany, in rest of world.

The trial will be conducted at approximately 50 sites in 6 countries in Europe.

The Coordinating Investigator represents all Investigators for decisions and discussions regarding this trial, consistent with the International Council for Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigator will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical trial report.

Signature pages for the Protocol Lead and the Coordinating Investigator as well as a list of Sponsor responsible persons are in Appendix B.

The trial will appear in the following clinical trial registries: Clinicaltrials.gov, EU clinical trial registry and national registries as per local regulations.

A contract research organization (CRO), PPD, will undertake the operational aspects of this trial with oversight by the Sponsor. Details of such structures and associated procedures will be defined in a separate Integrated Project Management Plan (IPMP). The IPMP will be prepared by the PPD Clinical Project Manager in cooperation with other PPD Operational Team Leads. Clinical quality assurance will be performed under the responsibility of the Development Quality Assurance department at Merck KGaA Darmstadt.

An Independent Data Monitoring Committee (IDMC) will be established to continually review available safety and tolerability data. The IDMC will be composed of independent physicians and an independent biostatistician. The full list of IDMC members and IDMC responsibilities will be included in the IDMC charter.

The investigational medicinal products (IMP) will be supplied by the Clinical Trial Supply Department of the Sponsor and packaged and labeled by PPD.

Details of structures and associated procedures will be defined in a separate Manual of Operations, which will be prepared under the supervision of the Clinical Trial Leader.

3 Background Information

3.1 Adalimumab

Adalimumab is a tumor necrosis factor (TNF) inhibitor indicated in the European Union (EU) and United States (US) for the treatment of multiple medical conditions, including rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), enthesitis-related JIA (EU only), psoriatic arthritis, ankylosing spondylitis, axial spondyloarthritis (EU only), Crohn's disease, ulcerative

4.2 Secondary Objectives

4.2.1 Key Secondary Objective

The key secondary objective is to compare the efficacy (ACR20) of MSB11022-[redacted] compared to Humira® at Week 12 in patients with moderately to severely active RA.

4.2.2 Other Secondary Objectives

Other secondary objectives are as follows:

- To evaluate the immunogenicity profile of MSB11022-[redacted] compared to Humira® in patients with moderately to severely active RA up to Week 52
- To further compare the efficacy and safety of MSB11022-[redacted] compared to Humira® in patients with moderately to severely active RA up to Week 52
- To compare quality of life (QoL) and physical function on MSB11022-[redacted] with Humira® in patients with moderately to severely active RA
- To compare injection site pain levels of MSB11022-[redacted] versus Humira®.

4.3 Exploratory Objective

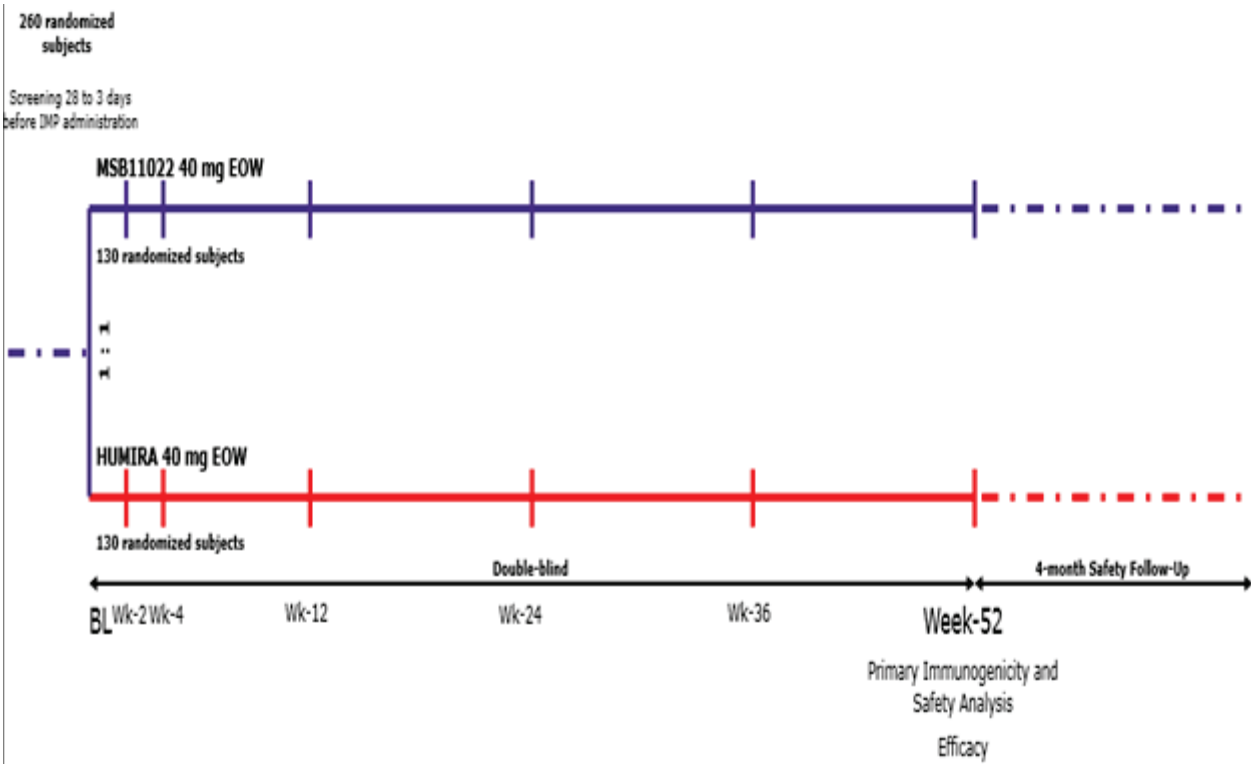
The exploratory objective is to evaluate population PK on MSB11022-[redacted] and Humira® in patients with moderately to severely active RA.

5 Investigational Plan

5.1 Overall Trial Design and Plan

A schematic of the trial design is presented in Figure 1.

Figure 1 Schematic of the Trial Design



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

5.2 Discussion of Trial Design

This trial is a two-arm, randomized, multicenter, double-blind, parallel group trial designed to compare the safety, immunogenicity, and efficacy of MSB11022-CCI with Humira® in approximately 260 randomized patients with moderately to severely active RA during a 52-week period.

Baseline is defined as the day on which the first dose of the IMP (blinded trial drug) is administered. The trial will include a pre-trial evaluation period (screening period, from 28 days to 3 days prior to IMP administration), a double-blind 48-week treatment period to evaluate long-term safety and immunogenicity, a 4-week safety follow-up visit, and a 4-month safety evaluation period.

Primary safety and immunogenicity endpoints will be assessed up to Week 52, key secondary efficacy endpoint will be assessed at Week 12. The analysis for the key secondary efficacy endpoint will be descriptive.

Re-screening will be allowed once for those patients who do not meet the inclusion/exclusion criteria within the above specified time limits. The Medical Monitor must promptly inform the Sponsor about requests and reasons for re-screening. An IDMC will review the safety data from this trial on an ongoing basis. Re-screened subjects will undergo all screening procedures.

Eligible patients will be randomized in permuted blocks in a 1:1 ratio by an interactive web response system (IWRS) to receive either MSB11022-CCI subcutaneous (s.c.) or Humira® s.c. at a dose of 40 mg every other week starting at baseline (Day 1/Week 0) up to and including Week 48. Patients will be stratified by the type of systemic therapy previously received: non-biological (biologic naïve patients) versus biological (biologic experienced patients). Patients who previously received both (biological and non-biological systemic therapies) will be assigned to the "biological" group. The exposure to previous biological agents will be limited to one TNF inhibitor other than adalimumab. The participation of patients in the previous biological systemic therapy stratum will be capped at 20% of the total number of patients randomized. This is in accord with what registered in other trials with biological agents in different rheumatic indications (63, 64, 65). Capping will be enforced through application of an IWRS.

The first 2 doses of IMP will be administered on site by the Investigator or other qualified personnel and the patient will be educated on the correct process. The third dose of IMP will be administered on-site by the patient. Patients will be monitored for 1 hour following the first 3 IMP administrations. If the Investigator judges it appropriate after proper training, the patient (or a caregiver) may continue to self-inject/inject the treatment for the remaining doses. Injection site pain will be assessed after doses 3 to 5. If a patient self-administers, the injection should not be given in the arm. The remaining doses of IMP will be dispensed, and written instructions on proper dosage, administration, storage, and recording will be provided to the patient/caregiver. Administrations performed at home will be recorded in a diary with the accurate dosing information (dosing date and time). In the case that there is a delay in the administration of IMP at home, there will be no delay to scheduled visits. During weeks with scheduled trial site visits, the IMP will be administered at the site.

The 48-week double-blind treatment period will allow for the collection of long-term comparative safety, immunogenicity, and efficacy data for MSB11022-CCI versus Humira®.

Patients who achieve less than 20% improvement in both swollen and tender joint counts at Week 24 (non-responders) will be discontinued from the IMP. These patients will remain in the trial safety analysis set and participate in the safety and immunogenicity assessments. For the management of these patients, see Section 5.4.1.

After Week 24, patients with less than 20% improvement in both swollen and tender joint counts at any scheduled visit up to Week 52 will also be discontinued. Patients may continue at Investigator discretion from Week 24 to Week 52 as long as they maintain more than 20% improvement in both swollen and tender joint counts.

Patients who discontinue from the study medication but remain in the trial and continue for the safety/immunogenicity visits before the Week 52 visit will immediately complete an Early Termination visit and return for a Safety/Follow-up visit 4 weeks after the last dose of IMP. During this 4-week Safety Follow-up period, no excluded treatment for RA (as defined in this protocol) should be administered. Patients will return for an additional safety evaluation 4 months after the last dose of IMP. Treatment for RA from the 4-week Safety Follow-up visit to the 4-month Safety Evaluation visit will be at the discretion of the Investigator following institutional standard of care. The 4-week and 4-month Safety Follow-up visits will not be duplicated if either of these visits falls within 2 weeks of an otherwise scheduled visit. If the 4-week and 4-month Safety Follow-up

over the entire duration of the study. Previous treatment with up to 4 disease-modifying antirheumatic drugs (DMARDs) including MTX is allowed. Up to 20% of patients may have been treated with 1 TNF inhibitor (other than adalimumab, adalimumab biosimilar investigational products, or innovator investigational products). This patient population was chosen because it was the most robustly studied population in Phase III studies and likely represents the majority of patients receiving adalimumab. Additionally, as confirmed in a recent EMA consultation (April 2016), RA represents a sensitive setting to investigate potential differences in immunogenicity (28).

The inclusion and exclusion criteria (see Sections 5.3.1 and 5.3.2, respectively) have been chosen to ensure patient safety by identifying patients with a history of specific medical conditions or those receiving specific medications that may pose a risk based on the mechanism of action of this class of drugs.

5.2.2 Justification for Dose

The dose and regimen selected are those approved for Humira® for the treatment of RA.

5.2.3 Rationale for Endpoints

5.2.3.1 Primary Endpoint

Incidence of AESI (Hypersensitivity) including and up to Week 52

In order to provide long-term safety and immunogenicity data in patients to support the new CCI formulation, this descriptive study will evaluate the safety and immunogenicity profile of MSB11022-CCI compared to the Humira® in patients with moderately to severely active RA who have had an inadequate response to MTX. In such a population, the rate of most commonly observed hypersensitivity events is 26.5% for the injection site reactions and 11% for rash (29).

5.2.3.2 Key Secondary Endpoint

The endpoints and schedule for the efficacy assessment reflect the most up-to-date regulatory guidance and evidence-based recommendations for this indication (30, 31). Additionally, an intensive efficacy assessment up to Week 12 is appropriate to properly evaluate the response curves before a plateau is reached.

American College of Rheumatology 20% response criteria (ACR20) – An ACR20 response, the most extensively used criterion for response in RA, is defined as an improvement of at least 20% in the number of tender joints and swollen joints, and at least 20% improvement in 3 out of the remaining 5 ACR core-set measures (patient assessment of arthritis pain, Patient's and Physician's Global Assessment of Disease Activity, physical function [HAQ-DI], and acute phase reactants). Data on efficacy and safety of adalimumab in combination with MTX against placebo, in patients affected by RA, were mainly evaluated from 6 multicenter, randomized, double-blind, controlled studies (29, 32, 33, 34, 35, 36). These trials were all conducted in adult RA patients with long-standing, moderately to severely active disease. ACR20 has been extensively studied

also in the recent Amgen's proposed biosimilar adalimumab ABP501 (37), Samsung's proposed biosimilar adalimumab SB5 (38), Celltrion's biosimilar infliximab CT-P13 (39).

5.2.3.3 Other Secondary Endpoints

Safety

Incidence of TEAEs and SAEs including and up to Week 52

In a population of MTX insufficient responders, the rate of TEAEs and SAEs at Week 52 has been reported up to 91% and 15-17%, respectively (40, 41, 42).

Immunogenicity

Numbers of patients who develop ADA, the ADA titer, and numbers of patients who develop anti-adalimumab neutralizing antibodies

An important objective of this clinical study is to investigate whether the CCI based formulation of MSB11022 displays a comparable immune response when compared to Humira®. The appearance of an immune response will be assessed in terms of formation of anti-drug-antibodies (ADA) and in terms of clinical manifestations.

Efficacy

ACR50, ACR70 – These are defined as an improvement of at least 50% and 70% respectively, in the number of tender joints and swollen joints, and at least 50% (ACR50) and 70% (ACR70) improvement in 3 out of the remaining 5 ACR core-set measures (patient pain, Patient's and Physician's Global Assessment of Disease Activity, physical function, acute phase reactants, respectively).

DAS28-ESR – The Disease Activity Score calculated on 28 joints (DAS28-ESR) is a composite score derived from 4 measures (43). Components of DAS28-ESR are:

- The number of swollen joints (out of the 28),
- The number of tender joints (out of the 28),
- Erythrocyte sedimentation rate (ESR),
- Patient's Global Assessment of Disease Activity on a visual analog scale (VAS).

The results are then fed into a formula to produce the overall disease activity score. A DAS28-ESR of > 5.1 implies active disease, < 3.2 low disease activity, and < 2.6 remission. A change of 1.2 (twice the measurement error) is defined as a significant change of the disease activity state (44). Yet, a change of 0.6 may be already be considered as a clinically meaningful variation in the context of defining response to therapy: indeed DAS28 is the core element of the EULAR response criteria. It is validated for use in clinical research and it is extensively used in clinical practice as well (45).

SDAI – The Simplified Disease Activity Index (SDAI) is the numerical sum of 5 outcome parameters: tender and swollen joint count (based on a 28-joint assessment), Patient's and

Physician's Global Assessment of Disease Activity (VAS) and level of CRP (mg/dL, normal < 1 mg/dL). The SDAI is a valid and sensitive assessment of disease activity and treatment response that is comparable with the DAS28 and ACR response criteria; it is easy to calculate and therefore a viable tool for day-to-day clinical assessment of RA treatment (46, 47).

CDAI – The Clinical Disease Activity Index (CDAI) is a composite index (without acute-phase reactant) for assessing disease activity. CDAI is based on the simple summation of the count of swollen and tender joint counts of 28 joints along with Patient's and Physician's Global Assessment of Disease Activity (VAS) for estimating disease activity. The CDAI ranges from 0 to 76. The greater advantage associated with CDAI is its potential to be employed in evaluation of patients with RA consistently with close frequency and independently of any calculating device, therefore, it can essentially be used everywhere and anytime for disease activity assessment in RA patients (46, 47).

ACR/EULAR Boolean remission – Following the Boolean-based definition of remission of ACR/EULAR, at any time point, a patient must satisfy all of the following: tender joint count ≤ 1, swollen joint count ≤ 1, CRP ≤ 1 mg/dL, and Patient's Global Assessment Of Disease Activity ≤ 1 (0-10 VAS). The Boolean criteria appear more stringent than the DAS28 remission and have been specifically created for use in clinical trials (48). Emery et al. showed that a significantly greater proportion of patients achieved remission when receiving a combination of a TNF inhibitor (golimumab) in combination with MTX as compared with those receiving MTX monotherapy (49).

Quality of Life (QoL)

HAQ-DI – The Health Assessment Questionnaire-Disability Index is a validated patient reported outcome measure for the evaluation of physical function. There are 8 sections: dressing, arising, eating, walking, hygiene, reach, grip, and activities. There are 2 or 3 questions for each section. Scoring within each section is from 0 (without any difficulty) to 3 (unable to do). For each section, the score given to that section is the worst score within the section, eg, if 1 question is scored 1 and another 2, then the score for the section is 2. In addition, if an aid or device is used or if help is required from another individual, then the minimum score for that section is 2. If the section score is already 2 or more then no modification is made. The 8 scores of the 8 sections are summed and divided by 8. The result is the disability index (DI) or functional disability index (FDI) (50). The HAQ-DI has been validated for use in RA over 3 decades (51).

36-item Short-Form Health Survey – The Short Form (36) Health Survey (SF-36) is a validated 36-item, patient-reported indication of overall health status not specific to any age, disease or treatment group (52). It has been extensively studied in RA, and a significant association between the physical functioning score of the SF36 and the HAQ-DI score, as well as with other measures of disease activity and severity, and co-morbidities has been demonstrated (53).

The SF-36 includes 1 multi-item scale measuring each of the following 8 health concepts: (1) physical functioning; (2) role limitations because of physical health problems; (3) bodily pain; (4) social functioning; (5) general mental health (psychological distress and psychological wellbeing); (6) role limitations because of emotional problems; (7) vitality (energy/fatigue); and (8) general health perceptions.

infectious disease specialist/pulmonologist as necessary in order to assess whether TB re-activation occurred during the trial.

If a patient develops active TB disease during the trial, treatment with IMP should be stopped immediately.

6.5 Packaging and Labeling of the Investigational Medicinal Product

MSB11022-CCI drug product will be manufactured by the Sponsor, and Humira® will be sourced by the Sponsor from a wholesaler. Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice guidelines.

Packaging of all IMPs for the trial will be done by the Sponsor's contract manufacturing organization, PPD.

MSB11022-CCI and Humira® will be provided in single-use prefilled syringes. Each prefilled syringe with plunger rod assembly will be packed in a carton box that will be closed with a tamper-evident seal. The IMPs will be packaged in a blinded fashion, or the sponsor will put in place a process to avoid any bias in the blinding. Full re-traceability according to current Good Manufacturing Practice guidelines will be provided based on the unique medication number on the labels together with packaging documentation.

The IMPs will be shipped and stored under controlled conditions according to the storage requirements (2°C to 8°C/36°F to 46°F).

The IWRS will support the logistics of the IMP.

6.6 Preparation, Handling, and Storage of the Investigational Medicinal Product

Handling instructions will be provided in a prepared handling guideline for MSB11022-CCI and in the Summary of Product Characteristics document for Humira®.

All IMPs must be stored in a secure area with limited access under controlled conditions at 2°C to 8°C/36°F to 46°F and protected from light. The IMP must not be frozen, and rough shaking of the solution must be avoided.

Patients or family members/caregivers who receive appropriate training will be permitted to administer medication in this trial. To ensure compliance with recommended storage conditions, all patients will be provided with cooler bags to transport the IMP home. Patients will be provided with instructions on proper storage, including instructions to store their trial treatment under refrigeration at 2°C to 8°C (36°F to 46°F) and not to leave their medication unattended or in a place that might get too hot, eg, inside a car. Patients should have access to refrigeration to store the IMP. Patients will also receive sharps containers and handling instructions.

virus tests will be performed for all screening patients as these conditions are trial entry exclusion criteria (see Section 5.3.2). Testing for TB will be performed as described in the exclusion criteria.

Patients who do not meet the inclusion/exclusion criteria within the specified time limits (ie, 28 days to 3 days prior to drug administration) and fail screening may undergo re-screening once, if approved by the Medical Monitor. If the patient is re-screened, the patient will receive a new patient identification number and will be asked to sign a new ICF. Such re-screened patients will undergo complete screening assessments.

Patients with 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 clinically insignificant intermittent condition. If testing is repeated for such patients, all screening tests will need to be repeated except for the chest X-ray, ECG, TB test, HIV, and hepatitis testing, which may be repeated separately from the other tests as necessary. The Medical Monitor may also give permission for tests to be repeated separate from other tests as necessary. 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 trial. Repeat tests should be conducted and results available within 28 to 3 days prior to baseline.

7.1.2 Baseline Assessments and Treatment Period

During the 52-week period, patients will be asked to visit the trial site at the visits indicated in the Schedule of Assessments (Table 1). Except for the Day 1/Week 0 (baseline) visit, a time window of up to 2 days before or after (±2 days) the scheduled day will be permitted for all trial visits during the treatment period.

Demographics, medical history, and inclusion/exclusion criteria will be reviewed to ensure that patients remain eligible for the trial.

An Emergency Medical Support card will be handed out on Day 1/Week 0 (baseline).

The IWRS will be contacted on Day 1/Week 0 (baseline) for patient randomization after all eligibility criteria have been confirmed. Patients will be randomized to receive either 40 mg MSB11022-CCI or 40 mg Humira® every other week starting on Day 1/Week 0 (baseline) and continuing up to and including Week 48. If the IMP is well tolerated as per medical judgment, and reflects the expected safety profile during these visits, the remainder of the patients will be dosed. The IMP is administered at the trial site for the first 3 doses; at Weeks 0, and 2, the patient or a caregiver will be trained for self-injection/injection and at Week 4, the patient will self-inject. Patients will be monitored for 1 hour following IMP administration on Day 1/Week 0, Week 2, and Week 4. Patients or their caregivers will administer the IMP for all subsequent doses and record the dosing date and time in a diary.

Patients who achieve less than 20% improvement in both swollen and tender joint counts at Week 24 (non-responders) will be discontinued from IMP and must immediately perform the assessments listed for the early termination visit and return for the safety follow-up visit 4 weeks after the last dose of IMP in addition to a safety follow-up visit 4 months after the last dose of IMP.

Patients who discontinue from the study medication (but remain in the trial and continue safety/immunogenicity visits) before the Week 52 visit will immediately complete an Early Termination visit and return for a Safety/Follow-up visit 4 weeks after the last dose of IMP. During this 4-week Safety Follow-up period, no excluded treatment for RA (as defined in this protocol) should be administered. Patients will return for an additional safety evaluation 4 months after the last dose of IMP. Treatment for RA from the 4-week Safety Follow-up visit to the 4-month Safety Evaluation visit will be at the discretion of the Investigator following institutional standard of care. The 4-week and 4-month Safety Follow-up visits will not be duplicated if either of these visits falls within 2 weeks of an otherwise scheduled visit. If the 4-week and 4-month Safety Follow-up visits since last IMP are completed within the 52 week visit schedule, these will not be repeated thereafter.

7.1.3 Early Termination Visit

Patients who discontinue the trial for any reason other than consent withdrawal before the Week 52 visit must undergo an early termination visit immediately upon discontinuation.

Assessments scheduled during the early termination visit are presented in Table 1.

7.1.4 Safety Follow-up Period

All patients will have a subsequent safety follow-up visit scheduled 4 weeks (±1 week) after the last dose of IMP, in addition to a safety follow-up visit 4 months (±1 week) after the last dose of IMP. The assessment for these visits are presented in Table 1.

7.2 Demographic and Other Baseline Characteristics

7.2.1 Demographic Data

At screening, the following demographic data will be collected: date of birth, sex (gender), race, and ethnicity.

7.2.2 Medical History

A complete medical history of each patient will be collected and documented during screening, which will include, but may not be limited to, the following:

- Past and concomitant diseases (nonmalignant and malignant) and treatments
- All medications (including herbal medications) taken and procedures carried out within 28 days prior to screening. The site should document any biologic ever used by the patient.

For trial entry, all of the patients must fulfill all inclusion criteria described in Section 5.3.1, and none of the patients should fulfill any exclusion criterion from the list described in Section 5.3.2. Significant findings that are observed after the patients signs the ICF and that meet the definition of an AE must be recorded in the AE section of the CRF.

7.3.1.1 American College of Rheumatology Response Rates

The individual components that make up the ACR Core Set of measures for RA are described below. Relief of signs and symptoms will be assessed using the ACR Responder Index, a composite of clinical, laboratory, and functional measures in RA. The ACR responses are presented as the minimal numerical improvement from baseline in multiple disease assessment criteria. The response criteria is based on the 68-joint tender/painful joint count, the 66-joint swollen joint count, and the CRP level.

ACR Core Set

a. Tender Joint Count (TJC)

For ACR measures, the number of tender and painful joints will be determined by examination of 68 joints (34 joints on each side of the patient's body; see Appendix D). The 68 joints to be assessed and classified as tender or not tender include: 2 temporomandibular joints, 2 sternoclavicular joints, 2 acromioclavicular joints, 2 shoulder joints, 2 elbow joints, 2 wrist joints, 10 metacarpophalangeal joints, 2 interphalangeal joints of the thumb, 8 proximal interphalangeal joints of the hands, 8 distal interphalangeal joints of the hands, 2 hip joints, 2 knee joints, 2 ankle joints, 2 tarsus, 10 metatarsophalangeal joints of the feet, 2 great toes (first proximal interphalangeal joint of the feet), and 8 proximal interphalangeal joints of the feet.

Joints will be assessed for tenderness by pressure and joint manipulation on physical examination. The patient will be asked for pain sensations on these manipulations and watched for spontaneous pain reactions. Any positive response on pressure, movement, or both will then be translated into a single tender-versus-nontender dichotomy. Joint assessments of 1 particular patient should be performed (if at all possible) by the same assessor throughout the trial to minimize inter-observer variation.

Missing, replaced, ankylosed, or arthrodesed joints will be identified by the Investigator at the screening visit and will be excluded from evaluation during the trial. The locations (or a listing) of surgical procedures should be documented in the patient's source documents/CRF pages.

b. Swollen Joint Count (SJC)

For ACR measures, the number of swollen joints will be determined by examination of 66 joints (33 joints on each side of the patient's body). The 66 joints to be assessed and classified as swollen or not swollen include: 2 temporomandibular joints, 2 sternoclavicular joints, 2 acromioclavicular joints, 2 shoulder joints, 2 elbow joints, 2 wrist joints, 10 metacarpophalangeal joints, 2 interphalangeal joints of the thumb, 8 proximal interphalangeal joints of the hands, 8 distal interphalangeal joints of the hands, 2 knee joints, 2 ankle joints, 2 tarsus, 10 metatarsophalangeal joints of the feet, 2 great toes (first proximal interphalangeal joint of the feet), and 8 proximal interphalangeal joints of the feet.

Joints will be classified as either swollen or not swollen. Swelling is defined as palpable fluctuating synovitis of the joint. Swelling secondary to osteoarthrosis will be assessed as not swollen, unless

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If a particular AE's severity is not specifically graded by the guidance document, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment.

The 5 general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate
- Grade 3 or Severe
- Grade 4 or Life-threatening
- Grade 5 or Death

Investigators must also systematically assess the causal relationship of AEs to IMP(s)/study treatment (including any other non-IMPs, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMP include, but may not be limited to, temporal relationship between the AE and the IMP, known side effects of IMP, medical history, concomitant medication, course of the underlying disease, trial procedures.

Unrelated: Not reasonably related to the IMP. AE could not medically (pharmacologically/clinically) be attributed to the IMP under study in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the IMP. AE could medically (pharmacologically/clinically) be attributed to the IMP under study in this clinical trial protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (for example, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (for example, anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- 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.)

recorded treatment administration time), its severity, its causal relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the IMP, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance can be found in the CRF Completion and Monitoring Conventions provided by the Sponsor.

7.4.2.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the patient is initially included in the trial (date of first signature of informed consent/date of first signature of first informed consent) and continues until the 4-month safety follow-up/end of trial visit.

Any SAE assessed as related to IMP and all AESIs must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMP.

7.4.2.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee using the SAE Report Form following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, an SAE Report Form must be provided immediately thereafter.

Relevant pages from the CRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the CRF.

The Investigator must respond to any request for follow-up information (for example, additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE 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 safety reporting obligations.

Requests for follow-up will usually be made via the responsible Monitor, although in exceptional circumstances the Global Drug Safety department may contact the Investigator directly to obtain further information or to discuss the event.

Adverse Events of Special Interest

The AESIs have to reported in an expedited manner (like the SAEs outlined above) using the AESI form.

7.4.2.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving trial patients to the IEC/IRB that approved the trial.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of "findings that could adversely affect the safety of patients, impact the conduct of the trial or alter the IEC's/IRB's approval/favorable opinion to continue the trial." In particular and in line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor/designee will provide 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 Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For trials covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

7.4.2.6 Monitoring of Patients with Adverse Events

AEs are recorded and assessed continuously throughout the trial (see Section 7.4.2.3) and are assessed for final outcome at the 4-month safety follow-up visit. All SAEs ongoing at the 4-month safety follow-up visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the patient is documented as "lost to follow-up." Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.4.3 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to trial treatment (for example, resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the period defined in Section 7.4.2.4 must be recorded by convention in the AE page/section of the CRF. The same rule applies to pregnancies in female patients and to pregnancies in female partners of male patients. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 7.4.2.4.

Investigators must actively follow up, document, and report on the outcome of all these pregnancies, even if the patients are withdrawn from the trial.

The Investigator must notify the Sponsor/designee of these outcomes using the paper Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the patient sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 7.4.2.4, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a patient occurring during the course of the trial, the patient must be discontinued from IMP immediately. The Sponsor/designee must be notified without delay and the patient must be followed as mentioned above.

7.4.4 Clinical Laboratory Assessments

Blood and urine samples will be collected for the following clinical laboratory tests, following the timing noted in the Schedule of Assessments (Table 1) and sent to the central laboratory for analysis. All samples should be clearly identified.

The Sponsor should receive a list of laboratory normal ranges before shipment of trial drug. Any change in laboratory normal ranges during the trial should be forwarded to the Sponsor or designee in a timely manner.

For women of childbearing potential, a qualitative serum pregnancy test will be performed at screening only, and an on-site urine test will be performed at baseline, Weeks 4, 8, 12, 24, 36, 48, and 52, the early termination visit, and the safety follow-up visits. The dipstick and urine pregnancy testing will be done locally only. If abnormal dipstick findings are observed, a urine sample will be sent to the central laboratory for microscopy. When there is no site visit, the female patients will perform urine pregnancy tests themselves at home, ie, at Weeks 16, 20, 28, 32, 36, 40, and 44. The patient should be instructed to immediately contact the Investigator if she identifies a positive urine pregnancy test result.

The ESR will be assessed locally only.

Local clinical laboratory samples may be collected for emergency safety evaluations but are not required to be collected/recorded in the CRFs.

The blood samples listed in Table 3 will be drawn, processed, and stored in accordance with the directions provided in the Laboratory Manual (also see Appendix C).

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), basophils (absolute and percentage)
Biochemistry	Sodium, potassium, blood urea nitrogen, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, lactate dehydrogenase, serum albumin, calcium, phosphate, glucose, creatine kinase, uric acid, total bilirubin, total serum protein, cholesterol, triglycerides, C-reactive protein, coagulation (activated partial thromboplastin time and prothrombin time)
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 surface antigen, hepatitis B core antibody, hepatitis C antibody, HIV types 1 and 2
Other	Pregnancy test (women only), rheumatoid factor (RF), anti-citrillinated protein antibodies (ACPA), anti-nuclear antibody, anti-dsDNA, QuantiFERON Gold tuberculosis test

The following laboratory assessments will not be entered into the database: rheumatoid factor, pregnancy test, and viral serology.

7.4.5 Vital Signs, Physical Examinations, and Other Assessments

Vital signs including body temperature, respiratory rate, and heart rate (after 5-minute rest) will be measured once at screening and throughout the trial at the visits indicated in the Schedule of Assessments. Arterial blood pressure (after 5-minute rest) will be measured twice using a validated device and recorded at the visits indicated in the Schedule of Assessments (Table 1).

A complete physical examination (including, eg, 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 CRF. All clinically significant abnormalities occurring before signature of informed consent should be recorded in the Medical History section and/or Disease History; all abnormalities occurring or worsening after signature of informed consent should be recorded in the Adverse Events section. Abnormal findings are to be reassessed at subsequent visits.

Body weight will be recorded at screening and at subsequent visits as indicated in the Schedule of Assessments (Table 1) and documented in the CRF. Height will be measured at screening only.

A 12-lead ECG and chest X-ray will be recorded as indicated in the Schedule of Assessments (Table 1).

All newly diagnosed or worsening conditions, signs, and symptoms observed from screening, whether related to trial treatment or not, are to be reported as AEs.

For women of childbearing potential, a serum β-hCG pregnancy test will be carried out during the screening phase only, and a urine pregnancy test will be performed at the on-site visits (baseline, Weeks 4, 8, 12, 24, 36, 48, and 52, the early termination visit and the safety follow-up visit) and at home (Weeks 16, 20, 28, 32, 36, 40, and 44) as indicated in the Schedule of Assessments (Table 1).

7.5 Pharmacokinetics

The timing of sampling for PK analysis is based on available steady-state data from RA patients treated with 40 mg adalimumab s.c. These data showed that adalimumab steady-state concentrations were reached approximately 20 weeks after the beginning of adalimumab treatment (60, 61). Sparse sampling for population PK analysis will be collected in a subset of patients (at least 30/arm) in this trial.

All patients will have PK samples taken pre-first dose, and then prior to dosing on Weeks 2, 4, 12, 24, 36, and 52. In addition, a subset of 60 patients (30 per arm) will have additional samples to support the population PK analysis taken on Days 2 (24 h post first dose), 4, and 9, and Days 2 (24 h post Week 24 dose), 4, 9, and 14 (Week 26 pre-dose) after the Week 24 dose (see Table 2).

7.6 Biomarkers

Not applicable.

7.7 Other Assessments

Patient-reported outcomes (PROs) and the Physician's Global Assessment of Disease Activity will be assessed at the visits indicated in Table 1. The PROs consist of the HAQ-DI, Patient's Global Assessment of Disease Activity, Patient's Assessment of Arthritis Pain, SF-36, and EQ-5D-5L dimension instruments. The PRO/QoL questionnaires and the Physician's Global Assessment of Disease Activity are recommended to be completed prior to any of the other trial-related assessments being performed, that is, physical examinations, blood draws, trial treatment administration, etc. Data will be collected by the Contract Research Organization (CRO) and housed in a database. Validated translated versions of the PROs/QoL questionnaires will be used for each country participating in this trial

7.7.1 HAQ-DI

The HAQ-DI is a patient-reported questionnaire that is commonly used in RA to measure disease associated disability (assessment of physical function). It consists of several questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities (62, 63).

The disability section of the questionnaire scores the patient's self-perception on the degree of difficulty (0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do) covering the following domains: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and performing other daily activities. The reported use of special aids or devices and/or the need for assistance of another person to perform these activities is also assessed. The scores for each of the functional domains will be averaged to calculate the functional disability index.

7.7.2 Visual Analog Scales

Visual analog scales will include the Patient's and Physician's Global Assessment of Disease Activity, Patient's Assessment of Arthritis Pain and injection site pain.

Patient's Global Assessment of Disease Activity

The patient's overall assessment of his or her arthritis during the last 24 hours will be recorded using the horizontal VAS where the left end represents no disease activity (symptom free and no arthritis symptoms) and the right end represents maximum disease activity (maximum arthritis disease activity).

The patient will be asked to give an overall assessment of how the arthritis is affecting him/her at present by marking a vertical tick on a VAS from "no arthritis activity" to "extremely active arthritis."

Physician's Global Assessment of Disease Activity

The physician's overall assessment of the patient's arthritis during the last 24 hours will be recorded using the horizontal VAS where the left end represents no disease activity (symptom free and no arthritis symptoms) and the right end represents maximum disease activity (maximum arthritis disease activity).

The physician will give an overall assessment of how the arthritis is affecting the patient at present by marking a vertical tick on a VAS from "no arthritis activity" to "extremely active arthritis."

Patient's Assessment of Arthritis Pain

The patient will be asked to assess his or her current level of pain by marking a vertical tick on a horizontal VAS with the left end marked as "no pain" and the right end marked as "worst possible pain." The scale should be administered prior to the tender and swollen joint count examination.

- Immunogenicity
  - ADA to adalimumab and ADA titer including and up to Week 52
  - Neutralizing ADA to adalimumab including and up to Week 52
- Efficacy
  - ACR20 at Weeks 2, 4, 8, 24, and 52
  - ACR50 response rates at Weeks 2, 4, 8, 12, 24, and 52
  - ACR70 response rates at Weeks 2, 4, 8, 12, 24, and 52
  - Change from baseline in DAS28-ESR to Weeks 2, 4, 8, 12, 24, and 52
  - Proportion of patients with DAS28 low disease activity and remission at Weeks 2, 4, 8, 12, 24, and 52
  - Change from baseline in SDAI at Weeks 2, 4, 8, 12, 24, and 52
  - Change from baseline in CDAI at Weeks 2, 4, 8, 12, 24, and 52
  - ACR/EULAR Boolean remission rates at baseline, Weeks 2, 4, 8, 12, 24, and 52
- Quality of Life (QoL) and Physical Function

  At baseline, then at Weeks 12, 24, and 52:
  - HAQ-DI - Health Assessment Questionnaire – Disability Index
  - SF-36 - 36-item Short-Form Health Survey
  - EQ-5D-5L - The EuroQoL-5D-5L dimension instrument
- Injection site pain
  - Mean change in injection site pain on a VAS, evaluated during 3 (doses 3-5) administrations of IMP

8.3.3 Exploratory Endpoints

- Pharmacokinetic endpoints from a population PK analysis
  - Absorption profile characterization, if it is supported by the data
  - Apparent clearance (CL/F)
  - Apparent volume of distribution (Vz/F)
  - C_{trough} levels at Day 14 after first dose, at Weeks 4, 12, and 24 predose, and at Day 14 after dose at Week 24.

8.4 Analysis Sets

8.4.1 Enrolled

All participants who sign informed consent.

8.4.2 Intention-to-Treat

The Intention-to-Treat (ITT) Analysis Set will include all patients randomly allocated to a treatment, based on the intention to treat "as randomized" principle (ie, the planned treatment regimen rather than the actual treatment given in case of any difference). Patients will be analyzed according to their randomized treatment.

8.4.3 Per-Protocol

The Per-Protocol (PP) analysis set includes all randomized and treated patients (hence a subgroup of the ITT analysis set) who do not have any important clinical protocol deviations (67).

Patients will be analyzed according to their randomized and received treatment, as receipt of a different treatment from that assigned is an important protocol deviation.

The following are criteria for inclusion in the PP analysis set:

- Received the randomized treatment;
- Compliance with all entry criteria;
- Absence of important clinical trial protocol violations per regulatory definition;
- Adequate compliance with and sufficient exposure to IMP;

The criteria for the PP population will be defined in detail in the SAP; major protocol violators excluded from the PP analysis set will be identified.

Patients who achieve less than 20% improvement in both swollen and tender joint counts at Week 24 (non-responders) will be discontinued from the treatment. These patients will remain in the trial safety analysis set and participate in the safety and immunogenicity assessments.

8.4.4 Safety

The Safety Analysis Set will include all randomized patients who receive at least one dose of trial treatment. Patients will be analyzed according to the actual treatment they receive during the trial.

8.4.5 Population Pharmacokinetics

The Pharmacokinetic Analysis Set will include all patients who receive at least 1 dose of trial treatment and have at least 1 valid post-dose pharmacokinetic assessment without protocol deviations which could potentially affect PK.

Continuous outcomes (eg, DAS28, SDAI, and CDAI mean change from baseline) will be summarized using descriptive statistics.

The summaries will be presented on both the ITT and the PP analysis sets.

8.5.3.3 Analysis of Safety Endpoints

Safety endpoints below will be summarized by treatment group:

- Treatment-emergent AEs, SAEs, AESIs, and deaths
- Clinical laboratory values including hematology, chemistry, and urinalysis
- Vital signs
- Physical exam
- 12-lead ECG

Adverse events will be coded with the latest version of the Medical Dictionary for Regulatory Activities and summarized by treatment group overall, by severity, and by relationship to MSB11022-CCI [redacted] or Humira®.

The nature, severity and frequency of the adverse drug reactions in patients who received MSB11022-CCI [redacted] will be compared with those who receive Humira® to evaluate comparability of safety.

AEs and concomitant medications will be recorded at each visit: screening, baseline (Week 0), and Weeks 2, 4, 8, 12, 24, 36, 48, and 52.

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

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

All clinical laboratory data will be stored in the database in the units in which they were reported and using the laboratory reference ranges. Patient listings and summary statistics at each assessment time will be presented using the International System of Units (SI units). Laboratory data not reported in SI units will be converted to SI units before processing.

Safety endpoints will be analyzed using the safety analysis set.

8.5.3.4 Analysis of Quality of Life Endpoints

Patient reported outcomes (PRO) quality of life and physical function endpoints, HAQ-DI, SF-36, and EQ-5D-5L, at baseline and Weeks 12, 24, and 52, will be summarized using descriptive statistics.

The summaries will be presented using both the ITT and the PP analysis sets.

8.5.3.5 Analysis of Immunogenicity Endpoints

Descriptive statistics of the immunogenicity assessment per treatment arm will be given with reference to the Safety Analysis Set unless otherwise specified in the SAP.

- Number and percentage of ADA positive patients at any time
- ADA titer
- Number and percentage of NAb positive patients
- Time to ADA
- Change of titer over time
- Persistent or transient ADA for patients with a treatment period ≥ 6 months

Presentations will include summaries of PK, safety, and efficacy endpoints over time for ADA positive and negative patients.

Correlation of PK, safety, and efficacy endpoints versus treatment group split by upper and lower quartile patients, based on their maximum ADA titer values, may be presented as exploratory analyses.

ADA status, titer, and NAb status will be listed and summarized by treatment and time point of collection.

8.5.3.6 Analysis of Pharmacokinetic Endpoints

Serum concentrations of MSB11022-CCI and Humira® 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.

8.5.4 Analysis of Population Pharmacokinetics Endpoints

Pharmacokinetic parameters (absorption profile, apparent clearance, apparent volume of distribution, and C_{trough} levels) of MSB11022-CCI and Humira®, with their intra- and inter-individual variability in the patient population, will be derived by population PK data analysis using a nonlinear mixed effects modeling approach, based on sparse sampling. The influence of covariates, such as standard demographic covariates, treatment (MSB11022-CCI or Humira®), and immunogenicity, will be explored graphically and statistically to explain potential random inter- and intra-individual variability in PK parameters.

8.6 Interim and Additional Planned Analyses

No interim analyses are planned.

An IDMC will review the safety data from this trial on an ongoing basis.

8.7 Missing Data

Details of the handling of missing data for all secondary endpoints will be provided in the SAP. Sensitivity analyses for the key secondary endpoint based on different missing data mechanism assumptions may be explored and will be pre-specified in detail in the SAP and documented prior to database lock.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at the site and will ensure that the trial is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, ICH GCP, and any other applicable regulations. The Investigator must ensure that only patients who have given informed consent are included in the trial.

According to United States Code of Federal Regulations Part 54.2 (e), for trials conducted in any country that could result in a product submission to the United States Food and Drug Administration for marketing approval and could contribute significantly to the demonstration of efficacy and safety of an IMP (which are considered "covered clinical trials" by the FDA), the Investigator and all subinvestigators are obliged to disclose any financial interest which they, their spouses or their dependent children may have in the Sponsor or the Sponsor's product under study. This information is required during the trial and for 12 months following completion of the trial.

9.2 Patient Information and Informed Consent

An unconditional prerequisite for each patient prior to participation in the trial is written informed consent, which must be given before any trial-related activities are carried out. Adequate information must therefore be given to the patient by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained. Prior to blood sampling for immunogenicity assessment at screening, subjects must give written informed consent that their sample may be used to validate the assays used in the immunogenicity assessment. A separate specific ICF will be provided to subjects who agree to participate in the PK sub-trial.

A patient information sheet must be prepared in the local language in accordance with ICH GCP and will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential patient, the Investigator or a designate will inform the patient verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The patient will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

If permitted by national regulations, a person other than the Investigator may inform the patient about the trial and sign the ICF, as above.

After the information is provided by the Investigator, the ICF must be signed and dated by the patient and the Investigator.

Appendix E: Protocol Amendments and List of Changes

Previous Protocol Amendments

Table of Amendments

Amendment Number	Substantial (Y/N)	Date	Region or Country	Included in the current document (Y/N)
Amendment 1	N	31 January 2017	Germany	N
Amendment 2	N	11 July 2017	Global	Y

WBC	White Blood Cell
WOCBP	Woman of Childbearing Potential

Randomization will be stratified by the type of systemic therapy previously received: non-biological (biologic naïve patients) versus biological (biologic experienced patients). Patients who previously received both (biological and non-biological systemic therapies) will be assigned to the "biological" group. The exposure to previous biological agents will be limited to one tumor necrosis factor (TNF) inhibitor other than adalimumab. The participation of patients in the previous biological systemic therapy stratum will be capped at 20% of the total number of patients randomized. Capping will be enforced through application of an IWRS.

The first 2 doses of IMP will be administered on site by the Investigator or other qualified personnel and the patient will be educated on the correct process. The third dose of IMP will be administered on-site by the patient. Patients will be monitored for 1 hour following the first 3 IMP administrations. If the Investigator judges it appropriate after proper training, the patient (or a caregiver) may continue to self-inject/inject the treatment for the remaining doses. Injection site pain will be assessed after doses 3 to 5. If a patient self-administers, the injection should not be given in the arm. The remaining doses of IMP will be dispensed, and written instructions on proper dosage, administration, storage, and recording will be provided to the patient/caregiver. Administrations performed at home will be recorded in a diary with the accurate dosing information (dosing date and time).

The 52-week double-blind period will allow for the collection of long-term comparative safety, immunogenicity, and efficacy data for MSB11022-CCI versus Humira®.

Patients who achieve less than 20% improvement in both swollen and tender joint counts at Week 24 (non-responders) will be discontinued from the IMP. These patients will remain in the trial safety analysis set and participate in the safety and immunogenicity assessments. After Week 24, patients with less than 20% improvement in both swollen and tender joint counts at any scheduled visit up to Week 52 will also be discontinued. Patients may continue at Investigator discretion from Week 24 to Week 52 as long as they maintain more than 20% improvement in both swollen and tender joint counts.

Patients who discontinue from study medication (but remain in the trial and continue for the safety/immunogenicity visits) before the Week 52 visit will immediately complete an Early Termination visit and return for a Safety/Follow-up visit 4 weeks after the last dose of IMP. During this 4-week Safety Follow-up period, no excluded treatment for RA (as defined in this protocol) should be administered. Patients will return for an additional safety evaluation 4 months after the last dose of IMP. Treatment for RA from the 4-week Safety Follow-up visit to the 4-month Safety Evaluation visit will be at the discretion of the Investigator following institutional standard of care. The 4-week and 4-month Safety Follow-up visits will not be duplicated if either of these visits falls within 2 weeks of an otherwise scheduled visit. If the 4-week and 4-month Safety Follow-up since last IMP are completed within the 52-week visit schedule, these will not be repeated thereafter.

A subset of 60 patients (30 per treatment arm) will be randomly selected to participate in population PK analysis.

The anticipated duration of the entire trial is approximately 2 years.

Day/Week	Screening	Day 1 Week 0 (Baseline)	W2	W4	W6	W8	W12	W24[a]	W36	W48	W52[b]	ET[b]	4-week safety FU (4 weeks after last dose of IMP)[c]	4-month safety evaluation (4 months after last dose of IMP)[c]
Visit window (days)	-28 days to -3 days	None	± 2	± 2		± 2	± 2	± 2	± 2	± 2	± 2	± 7	± 7	± 7
Infectious disease specialist /pulmonologist consultation[v]											X		X	
SF-36[p]		X					X	X			X	X		
EQ-5D-5L[p]		X					X	X			X	X		
Collection and review of patient diary[w]						X	X	X	X	X		X		

ACPA = anti-citrullinated protein antibodies; B-hCG = beta-human chorionic gonadotropin; dsDNA = double-stranded DNA; ECG = electrocardiogram; EQ-5D-5L = EuroQol in 5 dimensions-5 levels; ET = early termination; FU = follow up; HAQ-DI = Health Assessment Questionnaire – Disability Index; SF-36 = 36-item Short Form Health Survey; RA = rheumatoid arthritis; RF = rheumatoid factor; VAS = visual analog scale; W = week.

a For patients who do not achieve a reduction in both swollen and tender joints of ≥ 20% at Week 24 or at any other later-scheduled time point, the IMP will be discontinued. These patients will remain in the trial safety analysis set and participate in the safety and immunogenicity assessments.

b The treatment termination information must be recorded during the Week 52 visit and the ET visit, and trial termination information must be recorded during the Safety Follow-up visit.

c Patients who discontinue from treatment will immediately have an ET visit and return for a safety follow-up visit 4 weeks after the last dose of IMP. Patients will return for an additional safety evaluation 4 months after the last dose of IMP. The 4-week and 4-month Safety Follow-up visits will not be duplicated if either of these visits falls within 2 weeks of an otherwise scheduled visit. If the 4-week and 4-month Safety Follow-up since last IMP are completed within the 52 week visit schedule, these will not be repeated thereafter.

d Medical history must include the following: disease phenotype, disease duration, infectious complications, disease localization, previous treatment(s) including identification of any previous biologic and nonbiologic RA therapy or history of treatment for latent or active TB, previous surgery/surgeries and smoking status.

e Review & update medical history only, to ensure patient remains qualified for the study.

f Screening results should be re-checked (particularly virus serology and TB tests) to ensure that the patient remains eligible for the trial.

g IMP will be administered every other week. During weeks with scheduled trial site visits, IMP will be administered at the site. During all other weeks, the patient (or a caregiver) will self-inject/inject IMP at home. Patients must be monitored for 1 hour following IMP administration on Day 1 of Week 0, Week 2, and Week 4. Last dose of IMP will be at Week 48.

h Height will be measured at screening only.

i Follicle-stimulating hormone test will be performed to confirm postmenopausal status of women with continuous amenorrhea ≥ 12 months.

j For women of child-bearing potential only, a qualitative serum pregnancy test will be performed at screening and an on-site urine test performed at baseline; Weeks 4, 8, 12, 24, 36, 48, and 52; the ET visit and the safety follow-up visit. When there is no site visit, the patients will perform urine pregnancy tests themselves at home, ie, at Weeks 16, 20, 28, 32, 40, and 44.

k RF and ACPA will only be collected at screening.

colitis, plaque psoriasis, pediatric plaque psoriasis (EU only), pediatric Crohn's disease, hidradenitis suppurativa, and uveitis. It is a recombinant human monoclonal antibody expressed in Chinese Hamster Ovary cells which binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the cell surface TNF receptors, p55 and p75.

MSB11022 is a proposed biosimilar of adalimumab (Humira®). To establish biosimilarity per international regulations, the biological product must be highly similar to the reference product notwithstanding minor differences in clinically inactive components and there must be no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product (1). Development of a biosimilar generally includes a comparison of the proposed product and the reference product with respect to structure, function, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity and clinical safety and effectiveness. If a product meets the requirements of biosimilarity and upon scientific justification, the potential exists for the proposed product to be approved for additional indications of use for which the reference product is approved. (2, 3, 4).

MSB11022 has previously undergone extensive analytical characterization compared to the reference product. In a recently conducted Phase I study, EMR200588-001, a citrate-based formulation (MSB11022-citrate) that showed a high degree of similarity has demonstrated PK similarity to the EU-approved and US-licensed reference products in healthy volunteers. In that study, the 90% confidence intervals (CIs) of the geometric least squares (LS) mean ratios (MSB11022-citrate/US-licensed Humira, MSB11022-citrate/EU-approved Humira®, and US-licensed Humira®/EU-approved Humira®) for area under the plasma concentration time curve from zero to the last measurable time point ($AUC_{[0\text{-last}]}$), area under the plasma concentration time curve from zero to infinity ($AUC_{[0\text{-inf}]}$), and maximum plasma concentration (C_{max}) were all entirely contained within the predefined equivalence interval of 80.00% to 125.00%. Therefore, MSB11022-citrate showed an equivalent PK profile to the 2 reference treatments, US-licensed Humira® and EU-approved Humira®; and US-licensed Humira® showed an equivalent PK profile to EU-approved Humira®, following a single subcutaneous (s.c.) injection administration of 40 mg. The safety and immunogenicity data supported the clinical similarity of MSB11022 to both US-licensed Humira® and also EU-approved Humira®.

EMR200588-002, a pivotal Phase III study designed to demonstrate equivalent efficacy of MSB11022-citrate versus EU-approved Humira® is currently ongoing in patients with moderate to severe chronic plaque psoriasis. Studies EMR200588-001 and EMR200588-002 will together constitute the core package for dossier submission for marketing authorization for the citrate-based formulation of MSB11022.

For potential commercialization, a new (CCI based) formulation has been developed. A thorough compatibility exercise has been performed between the two MSB11022 formulations, MSB11022-citrate and MSB11022-CCI Results from extensive characterization of the drug substance and product batches showed comparable characteristics. Therefore the product used in the Phase I EMR200588-001 and Phase III EMR200588-002 clinical trials is representative of the product, MSB11022-CCI to be used in the proposed Phase III MS200588-004 clinical trial. The planned MS200588-0004 study will use this new CCI formulation and will offer supportive

since last IMP are completed within the 52 week visit schedule, these will not be repeated thereafter.

All patients will have PK samples taken pre-first dose, and then prior to dosing on Weeks 2, 4, 12, 24, 36, and 52. In addition, a subset of 60 patients (30 per arm) will have additional samples to support the population PK analysis taken on Days 2 (24 h post first dose), 4, and 9, and Days 2 (24 h post Week 24 dose), 4, 9, and 14 (Week 26 pre-dose) after the Week 24 dose (see Table 2).

An IDMC will review the safety data from this trial on an ongoing basis.

Visit schedules for safety, immunogenicity, and efficacy assessments are detailed in the Schedule of Assessments in Table 1.

5.2.1 Scientific Rationale for Study Design

A double-blind, two-arm, parallel-group design represents an ideal setting to provide comparative long-term immunogenicity and safety data for the new CCI formulation versus Humira®.

Regulatory agencies are aware of the difficulty to power for safety and immunogenicity.

According to EMA "the investigation of safety is a multidimensional problem. Although some specific adverse effects can usually be anticipated and specifically monitored for any drug, the range of possible adverse effects is very large, and new and unforeseeable effects are always possible. Further, an adverse event (AE) experienced after a protocol violation, such as use of an excluded medication, may introduce a bias. This background underlies the statistical difficulties associated with the analytical evaluation of safety and tolerability of drugs, and means that conclusive information from confirmatory clinical trials is the exception rather than the rule. In most trials the safety implications are best addressed by applying descriptive statistical methods to the data, supplemented by calculation of confidence intervals wherever this aids interpretation." (20).

Concerning immunogenicity assessment, regulatory agencies currently prefer to focus on a comprehensive, yet descriptive, presentation and correlation of the immunogenicity data generated in clinical studies (21, 22, 23, 24, 25).

According to regulatory guidance and literature, data captured in the study should allow exploration of the possible correlation of the immunogenicity assessment to PK (eg, C_{trough}), safety (eg, injection site reactions), and/or efficacy (eg, reduced or loss of clinical response) (26, 27). In addition, the kinetics of an immune response (time to anti-drug antibodies [ADA], titer over time, persistent or transient ADA) observed will be used to compare the proposed biosimilar with the reference product to contribute to the totality of evidence and to the biosimilarity claim.

For all these reasons, the proposed study cannot be powered to demonstrate equivalence in safety and immunogenicity.

In this study, RA patients must have active disease, and be inadequate responders to methotrexate (MTX). The patients will continue to use MTX at a stable dose in combination with adalimumab

Questions in the standard version of the SF-36 refer to a 4-week time period. Scales are scored according to the Likert method. Lower scores equate to higher disability and higher scores equate to lower disability.

EQ-5D-5L – The EuroQoL-5 dimension-5 levels instrument is a short, easy to use, generic questionnaire used to measure health-related quality of life (HRQoL). It consists of a self-assessment questionnaire and VAS. It assesses the patient's current health in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The patient is asked to grade their own current level of function in each dimension into 1 of 5 levels (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems). The EQ-VAS is a self-rated health status using a vertical VAS. The EQ-VAS records the patient's perceptions of their own current overall health in a range from 0 (worst imaginable health state) to 100 (best imaginable health state) and can be used to monitor changes with time. The EQ-VAS addition to the EQ-5D-5L provides an insight into patients' perception of their own overall current health (54). EQ-5D-5L is also recognized by the National Institute of Health and Care Excellence (NICE) in the United Kingdom for monitoring HRQoL and is used in cost-utility analyses. The EQ-5D-5L is one the most extensively validated measures for use in patients with RA (55).

Evaluation of injection site pain – Information regarding injection site pain following s.c. injection with the MSB11022-CCI formulation vs. Humira® will be collected. The patient's reported perception of pain will be measured on a VAS where the slash drawn by the patient represents pain of increasing intensity (56). The first 2 injections will be administered by qualified personnel. The next three doses of IMP (3-5) will be self-administered by the patient and injection site pain will be assessed. Pain will be recorded immediately after, 15 minutes after, and 1 hour after the injections received by the patient.

CCI [redacted]

CCI [redacted]

[redacted]

The IMPs will be supplied in single-use prefilled 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).

In the event of a temperature deviation at the clinical site, the site must contact the clinical research associate without delay for further evaluation and assessment by the designated quality assurance personnel at Merck KGaA or their delegate. The medication with the temperature excursion should still be stored at the required temperature but quarantined during the investigations and must be appropriately labeled as "quarantine storage".

Additional details on the instructions for handling and storage will be described in the drug administration instructions and provided to patients as required for administration at home.

The IMP should not be administered after the date of expiration indicated on the product packaging.

6.7 Investigational Medicinal Product Accountability

The Investigator (or designee) is responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of records.

- Upon receipt of IMP, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation and storing it in the Pharmacy File as well as entering it into the IWRS.
- IMP dispensing, which will be triggered by the IWRS, will be recorded on the appropriate drug accountability forms so that accurate records will be available for verification at each monitoring visit.
- Trial site IMP accountability records will include the following:
  - Confirmation of IMP receipt, in good condition and in the defined temperature range.
  - The inventory of IMP provided for the clinical trial.
  - The use of each dose by each patient.
  - The disposition (including return, if applicable) of any unused IMP.
  - Dates, quantities, batch numbers, kit/syringe numbers, use-by dates, and the individual patient trial numbers.

The Investigator site should maintain records, which adequately document that patients were provided the doses specified in this protocol, and all IMPs provided were fully reconciled.

The IWRS should only be contacted after all scheduled assessments are completed and the patient's eligibility to remain in the trial is confirmed. Unused IMP must not be discarded or used for any purpose other than the present trial. No IMP that is dispensed to a different patient.

7.2.3 Tuberculosis Status

Assessment of TB status will be required before randomization.

7.2.3.1 Imaging

Bi-directional chest X-ray will be used to determine eligibility. If the QFT test is negative, a bi-directional chest X-ray, chest high-resolution CT, or chest MRI obtained within 12 weeks prior to randomization will be acceptable. If needed to rule out active TB, chest high-resolution CT or chest MRI could be subsequently performed.

If imaging evaluated by a qualified physician shows evidence of ongoing infectious disease, signs of active TB, or evidence of any malignant process, the patient will not be eligible to enter the trial.

7.2.3.2 QuantiFERON-TB Gold In-Tube assay

A QFT will be performed to assess the TB status during screening for all patients. Additional tests will be performed according to the Schedule of Assessments for patients whose previous QFT was negative. The QFT test will be supplied and analyzed by the central laboratory. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the Laboratory Manual. Refer to Section 6.4.3.1 for guidance on treatment for patients with TB.

7.2.4 Immunogenicity

A blood sample will be collected at screening for assay validation purposes only, no results will be reported and at baseline (on Day 1/Week 0 before IMP administration).

7.2.5 Other Baseline Assessments

All other baseline measurements, such as vital signs, a complete physical examination, clinical laboratory parameters, chest X-ray, and 12-lead ECG, will be assessed. Screening assessments will be rechecked to confirm eligibility for the trial. If the ECG findings are clinically relevant and would prevent the patient from participating in the trial, the patient should not receive IMP.

7.3 Efficacy Assessments

The following tests and procedures have been selected to evaluate the efficacy of MSB11022-CCI and describe clinical improvement in patients with RA and will be performed according to the Schedule of Assessments (Table 1).

7.3.1 Disease Activity Assessments

Assessments for RA disease activity will include ACR response criteria, DAS28-ESR, CDAI, and SDAI, which are described below.

there is unmistakable fluctuation. Joint assessments of 1 particular patient should be performed by the same assessor (if at all possible) throughout the trial to minimize inter-observer variation.

Missing, replaced, ankylosed, or arthrodesed joints will be identified by the Investigator at the screening visit and will be excluded from evaluation during the trial. The locations (or a listing) of surgical procedures should be documented in the patient's source documents/CRF pages.

Any joint which will have received an intra-articular steroid injection will be excluded by the joint count and will be documented as "not done" (ND) for the following 12 weeks. After this time the joint may be assessed again.

c. CRP

CRP will be the ACR Core Set measure of acute phase reactant. It will be measured at the central laboratory to help assess the effect of MSB11022-CCI or Humira® on the patient's RA.

ACR20

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

- TJC (68 joint count) and
- SJC (66 joint count) and
- An improvement of at least 20% in at least 3 of the following 5 assessments:
  - Patient's Global Assessment of Disease Activity
  - Patient's Assessment of Arthritis Pain
  - Patient's Assessment of Physical Function as measured by the HAQ-DI
  - Physician's Global Assessment of Disease Activity
  - Acute phase reactant as measured by CRP.

In this trial, ACR20 response calculations will use the HAQ-DI for the patient's assessment of physical function and CRP as the measure of acute phase reactant.

ACR50 and ACR70

ACR50 and ACR70 are defined in the same way as the ACR20 using at least 50% and 70% improvement, respectively.

7.3.1.2 DAS28-ESR

The DAS28-ESR is a measures of disease activity in 28 joints that consists of a composite numerical score of the following variables: TJC, SJC, or ESR, and Patient's Global Assessment of Disease Activity (57).

- Requires inpatient hospitalization or prolongs an existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is otherwise considered to be medically important. (Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may 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.)

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered an SAE, as described in Section 7.4.2.4.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (for example, undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline Medical Conditions, and are not to be considered AEs.

Adverse Events of Special Interest

The following is considered pre-defined AESIs for this trial:

Hypersensitivity (defined by Standardized MedDRA Query [SMQ] narrow as per the latest MedDRA version).

7.4.2.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the patient will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the patient's condition will be recorded as AEs, whether reported by the patient or observed by the Investigator.

Complete, accurate, and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the CRF. All SAEs must be additionally documented and reported using the appropriate SAE Report Form as described in Section 7.4.2.4.

It is important that each AE report include a description of the event, its duration (onset and resolution dates and times when it is important to assess the time of AE onset relative to the

Injection Site Pain

The patient's reported perception of pain will be measured on a VAS where the slash drawn by the patient represents pain of increasing intensity. The first 2 injections will be administered by qualified personnel. The next three doses of IMP (3-5) will be self-administered by the patient and injection site pain will be assessed. Pain will be recorded immediately after, 15 minutes after, and 1 hour after the injections received by the patient.

Results will be expressed in millimeters measured between the left end of the scale and the crossing point of the vertical line of the tick. This procedure is applicable for all VAS scales used in the trial.

7.7.3 SF-36

Patients will complete the SF-36 v2, standard version, a generic, health survey consisting of 36 questions, yielding 8 health-related quality of life (HRQoL) domains (physical functioning, role-physical, bodily pain, general health, vitality, social function, role emotional, mental health) as well as a psychometrically based physical component score (PCS) and mental component score (MCS).

7.7.4 EQ-5D-5L

Patients will complete the EQ-5D, a standardized measure of health status. It consists of 5 questions (mobility, self-care, usual activity, pain/discomfort and anxiety/depression) - the EQ-5D descriptive system, rated on a 5-point scale (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems) and a health state VAS of 0 (Worst imaginable health state) to 100 (Best imaginable health state).

8 Statistics

8.1 Sample Size

According to EMA recommendation (EMA/CHMP/SAWP/200743/2016), a total of 100 patients/arm should be adequate for a study primarily focusing on safety. To account for drop outs, this descriptive study will include 260 randomized patients in total (130/arm) in order to ensure 200 subjects in the study at Week 52. In fact, based on averaged originator's dropout rates at Week 52, a 20% rate of drop-out overall is included in the sample size (29, 40, 41). This sample size will permit an informative assessment of the occurrence of most common AESI (> 1/10) such as injection site reactions, and rash with a precision of 12.0% and 9.0% for the AESIs incidence of 26.0% and 11.0% respectively (29).

A subset of 60 patients (30 per treatment arm) will be randomly selected to participate in population PK analysis.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

Full details of all planned analyses will be provided in the SAP, to be finalized and approved prior to database lock.

Baseline is defined as the day on which the first dose of the IMP (blinded trial drug) is administered.

Descriptive statistics will be given with reference to the analysis set deemed appropriate for each particular endpoint.

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

- Continuous variables: n (number of non-missing observations), mean, standard deviation, 95% confidence interval (CI), median, minimum, and maximum
- Categorical variables: Frequencies and percentages
- Time to event variables: Kaplan-Meier estimates and 95% CIs

No correction for multiplicity is anticipated.

8.5.2 Analysis of Primary Endpoint

The primary safety (safety population) endpoint will be summarized by treatment group using the Safety analysis set. Incidence of AESIs and 95% CIs will be provided for each treatment group. Half width of 95% CIs for the difference in incidence for the most commonly observed clinical events of AESI (hypersensitivity) will also be calculated.

8.5.3 Analysis of Secondary Endpoints

8.5.3.1 Analysis of Key Secondary Efficacy Endpoint

The proportion of patients with an ACR20 response in both the treatment groups at Week 12 will be reported along with 95% CIs.

The analyses will be carried out on both the ITT and the PP analysis sets.

8.5.3.2 Analysis of Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints will be summarized descriptively according to the type of outcome.

The proportion of patients with ACR20, ACR50, and ACR70, DAS28 low disease activity and remission, and ACR/EULAR Boolean remission rates, will be reported along with 95% CIs.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and ICF should be provided to the patient prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the patient information sheet and any other written information to be provided to the patients and submit them to the IRB for review and opinion. Using the approved revised patient information sheet and other written information, The Investigator will explain the changes to the previous version to each trial patient and obtain new written consent for continued participation in the trial. The patient will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

9.3 Patient Identification and Privacy

A unique number will be assigned to each patient, immediately after informed consent has been obtained. This number will serve as the patient's identifier in the trial as well as in the clinical trial database. All patient data collected in the trial will be stored under the appropriate patient number. Only the Investigator will be able to link trial data to an individual patient via an identification list kept at the site. For each patient, original medical data will be accessible for the purposes of source data verification by the monitor, audits and regulatory inspections, but patient confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Patients will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

9.4 Emergency Medical Support and Patient Card

Patients will be provided with Emergency Medical Support cards supplied by the Sponsor for use during trial participation in order to provide clinical trial patients with a way of identifying themselves as participating in a clinical trial and to give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the patient. The information provided on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected patient. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (for example, unblinding) will follow the standard process established for Investigators.

In cases where the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor physician. This includes the provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician

Amendment No. 1

Scope Local (Germany)

Date of Protocol Amendment 31 January 2017

A summary of changes specific for Germany is included in the local German protocol V1.1.