Clinical Trial Protocol

Clinical Trial Protocol Number	MS200588-0004
Title	A multicenter, randomized, double-blind, phase III trial to evaluate the safety, immunogenicity, and efficacy of MSB11022 compared with Humira® in patients with moderately to severely active rheumatoid arthritis
Phase	III
IND Number	CCI [redacted]
EudraCT Number	2016-002852-26
Coordinating Investigator	PPD [redacted]
Sponsor	For sites in the US: EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike, Billerica, MA 01821, US For all countries except the US: Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany
Medical Responsible	PPD [redacted] Ares Trading S.A (an affiliate of Merck Serono S.A. – Merck Serono is a division of Merck) Z.I. de l'Ouriettaz 1170 Aubonne, Switzerland PPD [redacted]
Clinical Trial Protocol Version	11 July 2017 / Version 2.0 including Amendment 2
Replaces Version	09 September 2016 / Version 1.0

[redacted]

Protocol Table of Contents

Table of In-Text Tables

Table of In-Text Figures

List of Abbreviations

ACPA	Anti-citrillinated Protein Antibodies
ACR20	American College of Rheumatology 20% Response Criteria
ACR50	American College of Rheumatology 50% Response Criteria
ACR70	American College of Rheumatology 70% Response Criteria
ADA	Anti-drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANC	Absolute Neutrophil Count
ALT	Alanine Aminotransferase
ARA	American Rheumatology Association
AST	Aspartate Aminotransferase
$AUC_{(0\text{-last})}$	Area Under the Plasma Concentration Time Curve from Zero to the Last Measurable Time Point
$AUC_{(0\text{-inf})}$	Area Under the Plasma Concentration Time Curve from Zero to Infinity
CDAI	Clinical Disease Activity Index
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
CRF	Case Report Form
CRP	C-reactive protein
CT	Computerized Tomography
DAS28-ESR	Disease Activity Score Based on a 28 Joint Count
DMARDs	Disease-Modifying Antirheumatic Drugs
ECG	Electrocardiogram
EQ-5D-5L	Euro-Quality of Life – 5 Dimensions -5 Levels
EMA	European Medicines Agency
ESR	Erythrocyte Sedimentation Rate
EU	European Union
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
HIV	Human Immunodeficiency Virus

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

WBC	White Blood Cell
WOCBP	Woman of Childbearing Potential

1 Synopsis

Clinical Trial Protocol Number	MS200588-0004
Title	A multicenter, randomized, double-blind, Phase III trial to evaluate the safety, immunogenicity, and efficacy of MSB11022 compared with Humira® in patients with moderately to severely active rheumatoid arthritis
Trial Phase	III
IND Number	CCI [redacted]
FDA covered trial	Yes
EudraCT Number	2016-002852-26
Coordinating Investigator	PPD [redacted]
Sponsor	For sites in the US: EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike, Billerica, MA 01821, US For all countries except the US: Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany Medical Responsible: PPD [redacted] Ares Trading S.A, an affiliate of Merck Serono S.A Telephone: PPD [redacted]
Trial centers/countries	Approximately 50 trial sites in approximately 6 countries in Europe
Planned trial period (first patient in-last patient out)	First patient in: Quarter I 2017 Last patient out: Quarter III 2018
Trial Registry	All required registries

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.

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.

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

Planned number of patients: Approximately 260 randomized patients

Primary endpoint:

- Treatment-emergent adverse events of special interest (AESI) including and up to Week 52

Secondary endpoints:

Key secondary endpoint

- American College of Rheumatology 20% response criteria (ACR20) at Week 12 (An ACR20 response 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 via the Health Assessment Questionnaire-Disability Index [HAQ-D1], acute-phase reactants).

Other secondary endpoints

Safety

- Occurrences of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) including and up to Week 52
- Clinical laboratory values including hematology, chemistry, and urinalysis
- Vital signs
- Physical exam
- 12-lead electrocardiogram (ECG)

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
- American College of Rheumatology 50% Response Criteria (ACR50) and American College of Rheumatology 70% Response Criteria (ACR70) at Weeks 2, 4, 8, 12, 24, and 52
- Disease Activity Score based on a 28 joint count (DAS28)-ESR mean change from baseline at Weeks 2, 4, 8, 12, 24, and 52
- Proportion of patients with low disease activity as measured by DAS28-ESR, and remission at Weeks 2, 4, 8, 12, 24, and 52
- Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) mean change from baseline at Weeks 2, 4, 8, 12, 24, and 52

- ACR/European League Against Rheumatism (EULAR) Boolean remission rates at Weeks 2, 4, 8, 12, 24, and 52

Quality of life

- Health Assessment Questionnaire – Disability Index (HAQ-DI) questionnaire at screening, baseline, and Weeks 2, 4, 8, 12, 24, and 52
- 36-item Short Form Health Survey (SF-36) questionnaire at baseline and Weeks 12, 24, and 52
- Euro-Quality of Life – 5 Dimensions and 5-levels (EQ-5D-5L) questionnaire at baseline and Weeks 12, 24, and 52

Injection-site pain

- Mean change in injection site pain on a visual analog scale (VAS), evaluated during 3 administrations of IMP (doses 3 to 5) (immediately post-injection, 15 minutes post-injection, and 1 hour post-injection)

Exploratory endpoints

Population pharmacokinetics

- Absorption profile characterization, if it is supported by the data
- Apparent clearance (CL/F)
- Volume of distribution (Vz/F)
- C_{trough} levels at Day 14 after first dose, at Week 4, 12 and 24 pre-dose, and at Day 14 after dose of Week 24

Pharmacokinetics: 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).

Diagnosis and key inclusion and exclusion criteria:

Key inclusion criteria

Male or female patients ≥ 18 years old with a clinical diagnosis of moderately to severely active RA with disease duration of at least 6 months from confirmed diagnosis (defined by the 2010 revised ACR/EULAR 2010 criteria or the 1987 Criteria of American Rheumatology Association) despite methotrexate (MTX) therapy (defined as ≥ 6 swollen joints and ≥ 6 tender joints (from the 66/68 joint count system) at screening and randomization and either erythrocyte sedimentation rate (ESR) ≥ 28 mm/h or serum C-reactive protein (CRP) ≥ 1.0 mg/dL at screening. Patient must have been treated with MTX for a total of at least 12 weeks prior to baseline and must have been on both a stable route of administration (oral or parenteral) and stable dose of MTX (10 to 25 mg/week) for at least 4 weeks prior to screening. Patients must be adalimumab naïve and have discontinued infliximab (either originator or investigational or approved biosimilar), certolizumab pegol (either originator or investigational

or approved biosimilar) or golimumab (either originator or investigational or approved biosimilar) 8 weeks prior to screening, or etanercept (either originator or investigational or approved biosimilar) 4 weeks prior screening.

Key exclusion criteria

A patient will be excluded if he or she is considered ACR functional class IV as defined by the ACR classification of functional status or wheelchair/bedbound or has diagnoses of Felty's syndrome or any other inflammatory arthritides/systemic autoimmune disease other than secondary Sjögren's syndrome. The patient must not have received therapy with leflunomide within 12 weeks prior to baseline (Day 1); disease-modifying antirheumatic drugs other than MTX including but not limited to oral or injectable gold, sulfasalazine, azathioprine, penicillamine, cyclosporine, or tacrolimus within 4 weeks prior to baseline; or increasing doses of non-steroidal anti-inflammatory drugs (including low dose aspirin and COX-2 inhibitors) in the 2 weeks prior to baseline; had prior exposure to alkylating agents, such as chlorambucil or cyclophosphamide; use oral glucocorticoids > 10 mg/day prednisone or equivalent (dose must have been stable for the 4 weeks prior to baseline); or received any intra-articular, intravenous, or intramuscular use of corticosteroids in the 6 weeks prior to baseline. The patient will also be excluded if they have a history of an ongoing, chronic, or recurrent infectious disease (including active or latent tuberculosis [TB]); history of active or latent TB; or a history of hypersensitivity to any component of the IMP formulation, comparable drugs, or latex. The patient will be excluded if they have a concomitant diagnosis or history of congestive heart failure (New York Heart Association [NYHA] class III or IV).

Investigational Medicinal Product: dose/mode of administration/dosing schedule: MSB11022-CCI will be administered at a dose of 40 mg s.c. every other week starting from baseline.

Reference therapy: dose/mode of administration/dosing schedule: Humira® will be administered at a dose of 40 mg s.c. every other week starting from baseline.

Planned trial and treatment duration per patient: The planned trial duration per patient is approximately 17 months: a screening period of 28 days to 3 days prior to IMP administration, a double-blind 48-week treatment period to evaluate long-term safety and immunogenicity, a safety follow-up visit 4 weeks after the last dose of IMP, and an additional safety evaluation at 4 months following the last dose of IMP. During the 4-week Safety Follow-up period, no excluded treatment for RA (as defined in this protocol) should be administered. 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.

Statistical methods: 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. This sample size will allow to provide a precision of 12.0% (injection site reactions) and 9.0% (rash) for the AESIs incidence of 26.0% and 11.0% respectively.

Eligible patients will be randomized in a 1:1 ratio by an IWRS to receive either MSB11022-CCI s.c. or Humira® s.c. at a dose of 40 mg every other week starting at baseline

up to and including Week 48. Randomization will be stratified by the type of systemic therapy previously received. The participation of patients in the previous biological systemic therapy stratum will be capped at 20% of the total number of patients randomized.

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). 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 protocol deviations per regulatory definition.

The Safety Analysis Set will include all randomized patients who receive at least one dose of trial treatment. The PK 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.

Safety endpoints will be summarized by treatment group using the Safety analysis set. The incidence with 95% CI of AESIs will be provided for each treatment group. The half width of 95% CIs of the difference for the most common AESI incidence between the 2 treatment groups will also be calculated.

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

Descriptive statistics of the immunogenicity assessment per treatment arm will be given with reference to the Safety Analysis Set.

The proportion of patients with an ACR20 response in both the treatment groups at Week 12 as well as 95% CIs for their difference will be reported in the ITT and Per protocol analysis sets.

Table 1 Schedule of Assessments

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
Informed consent	X													
Demographics, medical history[d]	X	X[e]												
Inclusion/exclusion criteria	X	X[f]												
Randomization		X												
IMP dispensed[g]				X		X	X	X	X					
IWRS contacted	X	X	X	X		X	X	X	X	X				
Trial medication administered at site[g]		X	X	X		X	X	X	X	X				
Physical examination	X	X	X	X		X	X	X	X	X	X	X	X	
Vital signs (including blood pressure, height,[h] and weight, body temperature, respiratory rate, heart rate)	X	X	X	X		X	X	X	X	X	X	X	X	
Clinical chemistry, hematology, urinalysis	X	X	X	X			X	X	X	X	X	X	X	
Follicle-stimulating hormone test[i]	X													
Pregnancy test (serum β-hCG)[j]	X													
Urine pregnancy test[j]		X		X		X	X	X	X	X	X	X	X	
Antibody tests: ANA, anti-dsDNA, RF and ACPA[k]		X						X			X	X	X	

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

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.

l Blood samples for human immunodeficiency virus, hepatitis B virus, and hepatitis C virus will be obtained at screening.

m The tuberculosis Quantiferon-Gold test will only be performed in patients whose previous test was negative. Continuation of study medication will be excluded in patients who were QFT negative at randomization, but subsequently become QFT positive at Week 24.

n If a bi-directional X-ray is available from the last 3 months before planned randomization, the exam will not be repeated at screening.

o The ECG will be repeated at the ET or 4-week/4-month Safety/Follow-up visit only if in the opinion of the Investigator it is clinically warranted.

p Patient reported outcome questionnaires and the Physician's Global Assessment of Disease Activity must be performed prior to any other assessments at all visits.

q Performed locally.

r All blood samples for immunogenicity assessment and IMP concentration must be drawn prior to administration of the IMP, which will be performed at the site for these visits. The date and exact time of sample collection must be recorded.

s For assay validation purposes only, no result(s) will be reported.

t Injection site pain (VAS) immediately post-injection, 15 min post-injection, and 1 hour post-injection. If the pain has not resolved by 1 hour post-injection, the patients will be asked to record when the pain resolves. Injection site pain during 3rd, 4th, and 5th injection will be reported as adverse event similar to any injection site reactions at other time point of IMP administration. 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.

u Injection site pain will be recorded by the patient at home.

v Subjects who were QFT negative at randomization but subsequently become QFT positive at Week 24 or Week 52 will be referred by Investigators for a consultation with an infectious disease specialist/pulmonologist to assess whether TB re-activation occurred during the trial.

w Subject diaries will be collected at the visits indicated and reviewed by the site staff.

Table 2 Population PK Table of Assessments

Day/Week	Screening	Day 1 Week 0 (Baseline)	Day 2 Week 0	Day 4 Week 0	Day 9 Week 0	W2	W4	W6	W8	W12	W24	Day 2 Week 24	Day 4 Week 24	Day 9 Week 24	W26[+]	W36	W48	W52	ET	4-week safety FU (4 weeks after last dose of IMP)	4-month safety evaluation (4 months after last dose of IMP)
Population PK sampling[@]			X	X	X							X	X	X	X						

[@] Blood for population pharmacokinetic assessment will be collected in a subset of 60 patients (30 per treatment arm). Patients in the population PK analysis will have additional samples 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. The date and exact time of sample collection must be recorded.

[+] At Week 26 an additional sample for immunogenicity assessment is to be collected.

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

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

evidence by providing safety, immunogenicity, and efficacy data in a major approved indication for adalimumab, RA.

Refer to the Investigator's Brochure (IB) for further information about the nonclinical and clinical programs and guidance for the Investigator.

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP, and any additional applicable regulatory requirements.

Based on the available quality, nonclinical and clinical data to date, the conduct of the trial specified in this protocol is considered justified (see Section 5.2.1).

3.2 Rheumatoid Arthritis

Rheumatoid arthritis is a chronic autoimmune disorder affecting about 1% of the adult population worldwide (5). It is characterized by chronic inflammation of the synovial joints, particularly the small joints of hands and feet, which often leads to destruction of articular cartilage and juxta-articular bone. Most patients have a progressive course that eventually leads to considerable functional disability. A wide array of factors including geographical location, age, gender, infection, oxidative stress and genetic predisposition are known to be involved in the list of causative agents of RA (6, 7).

Juvenile idiopathic arthritis affects individuals up to 16 years of age, and often persists throughout adult life; both the systemic (sJIA) and the poly-articular (pJIA) forms of the JIA may be considered as the pediatric counterparts of the adult forms of RA. The destructive potential of both RA and JIA can be observed even in the earliest stage of the disease. While joints constitute the main target of the anatomical damage, both RA and JIA are systemic conditions and they are often accompanied by extra-articular manifestations such as fever, anemia, fatigue, and osteoporosis. The pathogenesis of these diseases is complex and involves both humoral and cellular reactions including immune-complex formation, vascular reactions and infiltration of lymphocytes and monocytes into the synovium. These infiltrating cells and synoviocytes release pro-inflammatory cytokines that perpetuate inflammation and destruction through effects on other cell types in the synovium and periarticular structures (8).

Reactive oxygen and nitrogen species have been shown to cause tissue injury and pathophysiological consequences in chronic inflammatory conditions such as RA and other rheumatic diseases (9). The basic pathology in the synovium of RA is hyperplasia, increased vascularity and inflammatory cell infiltration. The principal cells among the infiltrates are activated CD4+ T-cells which produce cytokines such as IL-1, IL-6 and TNF-α. TNF-α is a potent cytokine involved in normal inflammatory and immune response. Individuals with RA have high levels of TNF-α in the synovial fluid and it plays an important role in inflammation and joint destruction that are hallmarks of RA. Anti-TNF-α therapy induces a shift in the cytokine equilibrium producing more anti-inflammatory cytokines. Studies have demonstrated dramatic improvement in synovial inflammation in RA patients after treatment with neutralizing anti-TNF-α Abs or soluble TNF receptors, and decreased joint destruction after treatment with IL-1Ra. Immunosuppressive and anti-inflammatory cytokines, including TGFβ, IL-10 and IL-1Ra are highly and consistently expressed during RA synovitis. Production of these cytokines has been

proposed to reflect the patient's attempts to contain or control inflammation and achieve homeostasis (10).

In particular, IL-6 is a pleiotropic cytokine playing a pivotal role in the pathogenesis of both RA and JIA (11). For example its role for the process of B-cell maturation and the consequent production of auto-antibodies has been demonstrated. It also directly triggers the production of C-reactive protein (CRP) from hepatocytes. In animal models of autoimmune diseases, IL-6 also plays a critical role in the generation of Th17 pro-inflammatory lymphocytes. In patients with established RA, many of the articular and systemic manifestations could be explained by the biologic effect of IL-6 (8).

3.3 Safety and tolerability

The expected safety profile for MSB11022 is that known for EU-approved and US-licensed Humira®. The exclusion criteria for this trial take the known side-effect profile for adalimumab into consideration.

Adalimumab is known to compromise host defenses against pathogenic organisms, resulting in possible reactivation of tuberculosis (TB), invasive fungal infections, or susceptibility to opportunistic pathogens such as Legionella or Listeria. Upper respiratory tract and pulmonary infections feature prominently within the AE profile (12, 13, 14, 15, 16, 17, 18). Explicit screening for TB before exposure to Humira® is included in the trial procedures. No serious infections were reported in the first-in-human Trial EMR200588-001.

Minor differences in structural features such as glycosylation profiles cannot be excluded between 2 batches of closely related biological molecules targeting the same cell functions. For most biological systems, such minor variations is not expected to adversely impact the compound's ability to perform the biological role. In contrast, the immune system is uniquely sensitive to small biological variations and has the ability to distinguish between almost identical molecular entities. Accordingly, immunogenicity, such as anti-drug antibodies (ADAs), will be measured in this trial, and the results will be compared between the trial treatment arms. Differences in immunogenicity as ascertained in highly sensitive laboratory experiments may be indicative of a difference in the propensity to trigger clinically meaningful reactions of the immune system, eg, injection site reactions, or other forms of hypersensitivity (19).

The nonclinical pharmacodynamics properties of MSB11022 were investigated in vitro using binding and functional assays, which supported similarity of MSB11022 to Humira®. In addition, a comparative repeat-dose toxicity study was performed in a relevant animal model (cynomolgus monkeys), which proved comparability between MSB11022 and Humira®. Please refer to the current IB for complete nonclinical data.

MSB11022 was found to be equivalent in terms of PK to EU-approved Humira® and US-licensed Humira® and to have a comparable safety profile in Trial EMR200588-001.

In Trial EMR200588-001, no deaths and no SAEs related to the trial medications were observed. Similar proportions of subjects had treatment-emergent adverse events (TEAEs) in the MSB11022 trial arm (64.1%), the US-licensed Humira® arm (57.5%), and the EU-approved Humira® arm

(62.0%). Most of the TEAEs were considered to be mild in severity and not related to the trial medications. The most frequently reported TEAE considered to be related to the trial medications was headache.

No serious infections were reported in the trial. A higher proportion of subjects in the EU-approved Humira® arm had hypersensitive reactions compared with the other arms (2 subjects [2.6%] in the MSB11022 arm, 2 subjects [2.5%] in the US-licensed Humira® arm, and 6 subjects [7.6%] in the EU-approved Humira® arm).

No safety concerns based on laboratory measurements, vital signs, 12-lead electrocardiogram (ECG), or local tolerability were reported.

Please refer to the current IB for more details on the results of Trial EMR200588-001.

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP, and any additional applicable regulatory requirements.

3.4 Risk-Benefit Assessment

MSB11022 shows structural concordance with EU-approved and US-licensed Humira®, pointing towards a commonality of benefits and risks between them. It is thus expected that the benefits and the risks associated with MSB11022 are those described for EU-approved and US-licensed Humira®. Minor variations in the safety profile between Humira® and MSB11022 cannot be excluded due to subtle differences in micro-structure. Investigators should consider the known risks for Humira® as equally applicable for MSB11022.

The risk-benefit relationship was carefully considered in the planning of the trial. Based on the nonclinical data for MSB11022, the results of the PK equivalence Trial EMR200588-001, and clinical data for Humira® available to date, as well as the thorough comparability exercise which has been performed between the two MSB11022 formulations, MSB11022-citrate and MSB11022-CCI the conduct of this trial is considered justifiable using the dose and dosage regimen of the IMPs as specified in this clinical trial protocol. The trial will be discontinued in the event of any new findings that indicate a relevant deterioration of the risk benefit relationship and would render continuation of the trial unethical.

4 Trial Objectives

4.1 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 RA up to Week 52.

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

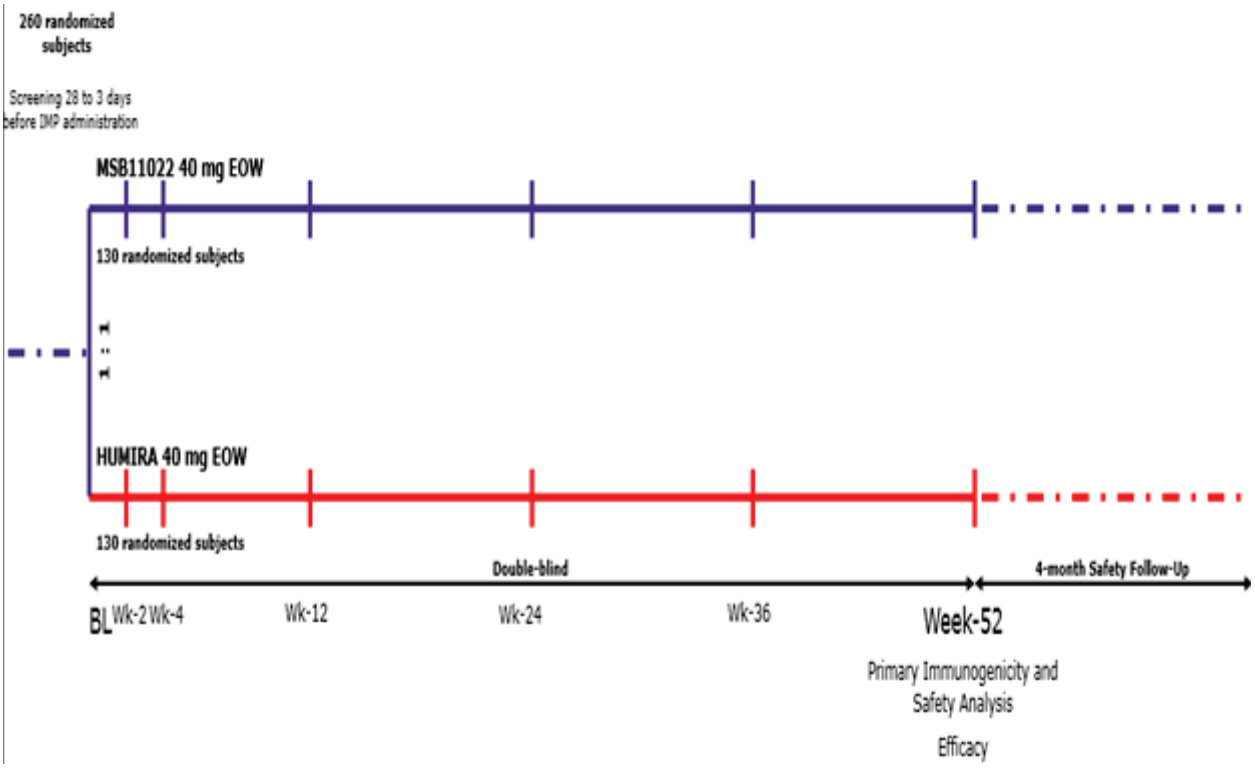
The exploratory objective is to evaluate population PK on MSB11022-[redacted] and Humira® in patients with moderately to severely active RA.

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

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

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.

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]

5.3 Selection of Trial Population

Only persons meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as patients. Prior to performing any trial assessments not part of the patient's routine medical care, the Investigator will ensure that the patient or the patient's legal representative has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

1. Must voluntarily give written informed consent. Patients must read and fully understand the Informed Consent Form (ICF) and the requirements of the trial and must be willing to comply with all trial visits and assessments.

2. Moderately to severely active diagnosis of RA with disease duration of at least 6 months from confirmed diagnosis, as defined by the 2010 revised ACR/EULAR 2010 criteria or the 1987 ARA criteria (Criteria of American Rheumatology Association) (present or past).

3. Have moderately to severely active disease despite MTX therapy defined as:

   a. ≥ 6 swollen joints and ≥ 6 tender joints (from the 66/68 joint count system) at screening and randomization.

   b. Either ESR (Westergren) ≥ 28 mm/h or serum CRP ≥ 1.0 mg/dL at screening.

4. Must have been treated with MTX for a total of at least 12 weeks prior to baseline and must have been on both: a stable route of administration (oral or parenteral) and stable dose of MTX (10 to 25 mg/week) for at least 4 weeks prior to screening.

5. Age 18 and older.

6. Must be adalimumab naïve and must not have received a non-marketed experimental biological agent for their RA in the past, or any biological agent not belonging to the class of TNF inhibitors. Patients who have received no more than 1 TNF inhibitor (either originator or investigational biosimilar candidate that underwent comparison with EU or US reference compounds) other than adalimumab are allowed to participate in the trial.

7. Must have discontinued infliximab (either originator or investigational or approved biosimilar), certolizumab pegol (either originator or investigational or approved biosimilar) or golimumab (either originator or investigational or approved biosimilar) 8 weeks prior to screening, or etanercept (either originator or investigational or approved biosimilar) 4 weeks prior screening.

8. A female patient is eligible to participate if she is not pregnant (see Appendix A), not breast feeding, and at least one of the following conditions applies:

   a. Not a woman of childbearing potential (WOCBP) as defined in Appendix A

OR

b. A WOCBP who agrees to use a highly effective contraception (ie, methods with a failure rate of less than 1% per year) as detailed in Appendix A of this protocol 3 months before the start of the first dose of the IMP, during the treatment period, and for at least 5 months after the last dose of the IMP.

9. Female patients must not be pregnant and if of childbearing potential, must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline before randomization.

10. Female patients must not be lactating or breast-feeding at screening through at least 5 months after the last treatment with IMP.

11. Male patients must be either surgically sterile (vasectomy with documented confirmation of aspermia) or must agree to use a condom and have their female partners use a highly effective contraception (ie, methods with a failure rate of less than 1% per year) as detailed in Appendix A for 3 months before the first dose of IMP, during the treatment period and for at least 5 months after the last dose of IMP, unless their partners are infertile or surgically sterile. Male patients must agree to continue to practice adequate contraception for 5 months after the administration of the IMP and refrain from donating sperm during this period.

12. Patient must be able and willing to self-administer s.c. injections.

5.3.2 Exclusion Criteria

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

2. A diagnosis of Felty's syndrome.

3. A diagnosis of any other inflammatory arthritides/systemic autoimmune disease other than secondary Sjögren's syndrome.

4. Received therapy with leflunomide within 12 weeks prior to baseline unless patient has undergone a drug elimination procedure with cholestyramine or activated charcoal powder, in which case the wash-out period is a minimum of 4 weeks.

5. Received DMARDs other than MTX including but not limited to oral or injectable gold, sulfasalazine, azathioprine, penicillamine, cyclosporine, or tacrolimus within 4 weeks prior to baseline. Patients may be taking oral hydroxychloroquine provided that the dose is not greater than 400 mg/day, or chloroquine provided that the dose is not greater than 250 mg/day and that doses have been stable for a minimum of 12 weeks prior to baseline. The hydroxychloroquine or chloroquine treatment will need to be continued at a stable dose for the duration of the study.

6. Received increasing doses of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (including low dose aspirin and COX-2 inhibitors) in the 2 weeks prior to baseline.

7. Prior exposure to alkylating agents, such as chlorambucil or cyclophosphamide.

8. Use oral glucocorticoids > 10 mg/day prednisone or equivalent. Doses up to 10 mg/day are allowed if have been kept stable for the 4 weeks prior to baseline.

9. Any intra-articular, intravenous, or intramuscular use of corticosteroids in the 6 weeks prior to baseline.

10. High potency opioid analgesics (eg, methadone, hydromorphone, oxycodone, fentanyl, or morphine) are prohibited during the study; other analgesics are allowed (eg, propoxyphene, tramadol, codeine, or aspirin), although not within 12 hours of study visits.

11. History of tuberculosis (TB), presence of active tuberculosis, or latent tuberculosis as detected by imaging (eg, chest X-ray, chest Computerized Tomography [CT] scan, Magnetic Resonance Imaging [MRI]) and/or positive QuantiFERON-TB Gold test (QFT) and/or clinical examination or has had latent TB disease at any time in the past.

    Patients will be evaluated for latent TB infection (LTBI) by the QFT enzyme-linked immunosorbent assay and by chest X-ray. If a patient tests positive for LTBI at screening, the patient will be screen failed and will not be randomized. Patients with indeterminate QFT test result may be re-tested once within the screening period:

    i. If the re-test is negative, the patient is eligible to take part in the trial.

    ii. If the re-test is positive, the patient will not be eligible to participate in the trial.

    iii. If the re-test is again indeterminate, the patient will be considered as having LTBI and will not be eligible to participate in the trial. No further QFT will be performed.

12. Received a live vaccine within 3 months prior to IMP administration or intends to receive a live vaccination during the trial or within 3 months after the last dose of IMP.

13. History of hypersensitivity to any component of the IMP formulation, comparable drugs, or latex.

14. Any infection as follows:

    a. Requires treatment with oral antibiotics within 14 days prior to IMP administration.

    b. A serious infection defined as requiring hospitalization or treatment with intravenous antibiotics within 8 weeks prior to IMP administration.

c. Has had herpes zoster or any opportunistic infection (eg, histoplasmosis, coccidioidomycosis, blastomycosis, pneumocystis, listeriosis, legionellosis, or parasitic infections) within 6 months prior to administration of IMP.

d. A history of persistent chronic infection or recurrent infections (3 or more of the same type of infection in any rolling 12 month period, eg, urinary tract or upper respiratory tract infections).

e. Have documentation of seropositivity for human immunodeficiency virus (HIV), or positive hepatitis C antibody test or hepatitis B surface antigen test and/or core antibody test for IgG and/or IgM or total Ig at screening.

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

16. Has a poorly controlled medical condition, such as but not limited to, poorly controlled diabetes, unstable ischemic heart disease, uncontrolled hypertension (systolic $\geq$ 160 mmHg and/or diastolic $\geq$ 95 mmHg), or other relevant medical disease, such as a neurological, pulmonary, gastrointestinal, or endocrine disease or a history of clinically significant hematological, renal, or liver disease or any other condition that, in the opinion of the Investigator, would put the patient at risk by participation in the trial.

17. Any major surgery (including arthroplasty) performed within the 6 weeks prior to the first dose of IMP.

18. Have presence of a solid organ or bone marrow transplant (with the exception of a successful corneal transplant > 3 months prior to screening).

19. Have a concomitant diagnosis or history of congestive heart failure (New York Heart Association [NYHA] class III or IV).

20. Have a known history, family history of or symptoms consistent with a demyelinating disease, such as multiple sclerosis, or optic neuritis, or symptoms suggestive of such a disorder.

21. Laboratory abnormalities deemed clinically significant by the Investigator or any of the following at screening:

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

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

c. Absolute neutrophil count (ANC) < 1.5 x 10^9/L.

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

e. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 times the upper limit of normal.

f. Creatinine > 1.5 mg/dL if < 65 years old, or > upper limit of normal if ≥ 65 or with proteinuria 4+ or greater by dipstick.

22. Women who are pregnant, lactating, or planning pregnancy within 6 months after the last dose of IMP.

23. Legal incapacity or limited legal capacity.

24. Patient is considered by the Investigator, for any reason, to be an unsuitable candidate for the trial.

25. Patient has participated in any nonbiological investigational clinical trial within 12 weeks or 5 drug half-lives (whichever is longer) before first administration of IMP in this trial or planned intake of an investigational drug during the course of this trial.

26. History of clinically significant drug or alcohol abuse within the last 2 years.

5.4 Criteria for Patient Withdrawal

5.4.1 Withdrawal from Trial Therapy

A patient will no longer receive the study medication in the event of any of the following circumstances:

a. Any events that unacceptably endanger the safety of the patient, including but not limited to the following:

- Use of prohibited treatment that in the opinion of the Investigator or Sponsor necessitates the patient treatment to be interrupted
- Occurrence of an exclusion criterion that is clinically relevant and affects the patient's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor
- Anaphylactic or other serious allergic reactions
- Development of active or latent TB
- New or worsening symptoms of congestive heart failure
- Biopsy confirmation of any malignancy other than non-melanoma skin cancer, such as basal cell carcinoma and squamous cell carcinoma.
- Symptoms suggestive of lupus-like syndrome
- Pregnancy

b. Interruption of MTX more than twice in a period of 4 weeks, or for a period of interruption longer than 4 months.

c. Noncompliance or protocol violations that in the opinion of the Investigator or Sponsor necessitates the patient being withdrawn. The decision to withdraw the patient should be taken in consultation with the Medical Monitor.

d. Participation in any other trial during the duration of this trial.

e. If the whole trial is discontinued prematurely.

f. Lost to follow-up.

If a patient is lost to follow-up, every possible effort must be made by trial center personnel to contact the patient and determine the reason for discontinuation. The measures taken to follow-up must be documented. If a patient discontinues before completion of trial procedures, the reason for discontinuation must be documented in the CRF and source documents.

Patients who discontinue from study medication (but 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. Subjects will return for an additional safety visit 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 visit since last IMP are completed within the 52 week visit schedule, these will not be repeated thereafter.

Withdrawn patients will not be replaced.

5.4.2 Withdrawal from the Trial

Patients may withdraw from the trial at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the trial. The Investigator should make every attempt to clarify the level of withdrawal: eg, whether or not banked samples can still be retained and evaluated, if the patient can still be contacted by phone for checking his/her status (eg, alive or not), or to return for safety visits. In case of withdrawal from the trial for reasons other than consent withdrawal, the assessments scheduled for the early termination visit should be performed immediately and return for a Safety/Follow-up visit 4 weeks after the last dose of IMP. Patients will return for an additional safety visit 4 months after the last dose of IMP. In any case, the appropriate CRF section must be completed. Patients will be asked to confirm that any samples collected but not yet analyzed can be utilized.

Patients withdrawn from IMP will continue the safety and immunogenicity follow-up until the end of the trial (also see Section 5.4.1 for specific details). These patients will be managed based on the Investigator's clinical judgment and per local guidelines, and any new medication prescribed in such a period will be recorded. In any case, the appropriate case report form (CRF) section must be completed.

5.5 Premature Termination of the Trial

The clinical trial may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavorable risk benefit judgment. The Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons, for poor enrollment, or because of discontinuation of clinical development of MSB11022 or withdrawal of Humira® from the market.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

5.6 Definition of End of Trial

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

6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term "IMP" refers to an active substance or a placebo being tested or used as a reference therapy in a clinical trial, including products that have a marketing authorization but are packaged or administered differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form.

6.1 Description of the Investigational Medicinal Product

CCI [redacted]

6.2 Dosage and Administration

MSB11022-CCI [redacted] will be administered at a dose of 40 mg s.c. every other week starting from baseline up to and including Week 48.

The Humira® will be administered at a dose of 40 mg s.c. every other week starting from baseline up to and including Week 48.

6.3 Assignment to Treatment Groups

A patient is eligible for randomization only if he/she fulfills all the inclusion criteria and none of the exclusion criteria and their eligibility is confirmed on Day 1/Week 0. The patient will be randomized by a central IWRS on Day 1/Week 0 after all eligibility criteria are confirmed in a 1:1 ratio to receive MSB11022-CCI or Humira® in a double-blind manner. Randomization will be stratified by the type of systemic therapy previously received.

A treatment kit labeled with individual kit/medication numbers will be provided to each trial site. See Sections 6.9 and 6.10 for methods of blinding and emergency unblinding. In the event of change in the reference product and the further supply is not guaranteed, the sponsor will have an established process to avoid any bias in the blinding. The IMP will be administered every other week. The IMP will be administered at the site at the visits indicated in the Schedule of Assessments after all assessments have been completed and the patient is determined to be eligible to remain in the trial. At each visit when IMP is dispensed, the trial staff will contact the IWRS after the Investigator confirms that the patient has met the criteria to continue in the trial to obtain appropriate kit numbers, and the specified kits will then be dispensed.

6.4 Concomitant Medications and Therapies

All concomitant medications taken by the patient during the trial, from the date of signature of informed consent are to be recorded in the appropriate section of the CRF, noting the name, dose, duration, and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention should also be recorded in the CRF.

6.4.1 Permitted Medicines

Permitted medicines will not be provided by the sponsor as they are considered standard of care background medications.

It is important that medication dosages taken during the study period remain stable. This includes, but it is not limited to, the dosage of corticosteroids and NSAIDs. However, reductions in these treatments will be allowed as clinically required for safety reasons.

Methotrexate: All patient should maintain a stable MTX dose (10 to 25 mg/week, PO, IM, or SC) during the study period. Any modification of the route of administration is not allowed. However, a dose reduction of MTX will be allowed in case of AEs. Temporary interruptions administration are allowed for up to 14 days (can be interrupted up to twice because MTX is administered once weekly). See withdrawal criteria related to interruptions in Section 5.4.1.

Folic Acid: It is possible that certain AEs that are commonly associated with MTX treatment occur. In order to minimize MTX toxicity, all patients treated with MTX should receive folic acid or equivalent at a dose of at least 5 mg/week according to local guidelines. This can either be given

as a single dose weekly or be divided into daily doses to achieve at least 5 mg folic acid per week. It is the Investigator's decision as to which dosing regimen is used.

Hydroxychloroquine or chloroquine: as per inclusion and exclusion criteria.

Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and NSAIDs are permitted during the study.

NSAID: patients may be treated with NSAIDs (including low dose aspirin and COX-2 inhibitors) for symptomatic treatment of their arthritis up to the maximum recommended dose per local labeling throughout the study (including COX-2 inhibitors). Drug must be at a stable dose for at least 2 weeks prior to baseline. Increases in the NSAID dose during the study are not allowed. However, discontinuation or reduction is allowed in case of NSAID-related toxicity. In patients who receive NSAIDs, prophylactic treatment with proton pump inhibitors or H2-receptor blockers is recommended.

NSAIDS, up to the maximum recommended dose per local labeling, are also allowed for the management of AEs not related to RA such as colds or sprains throughout the study (including COX-2 inhibitors).

Analgesics (other than NSAIDs) up to the maximum recommended doses may be used for pain control as required except for high potency opioids as delineated below. However, patients should not take analgesics within 12 hours prior to a visit where clinical efficacy assessments are performed.

Any medications that are considered necessary to protect patient welfare and will not interfere with the IMP may be given at the Investigator's discretion.

Rescue medications may be administered to address ineffective treatment, anticipated adverse reactions, or anticipated emergency situations.

Any concomitant medications (including over-the-counter medications, herbal medications, preventive vaccines, vitamins, and food supplements) and procedures must be recorded. A description of the type of drug or procedure, the amount, duration, reason for administration of drug, and the outcome of any procedure must be documented. AEs related to the administration of a concomitant medication or the performance of a procedure must also be recorded.

6.4.2 Prohibited Medicines

The use of prohibited medications will require the patient to be withdrawn from the IMP.

All biological and non-biological DMARDs other than MTX and hydroxychloroquine or chloroquine are prohibited during the study and must be discontinued prior to the initiation of IMP in accordance with specifications as per the inclusion and exclusion criteria.

High potency opioid analgesics (eg, methadone, hydromorphone, oxycodone, fentanyl, or morphine) as per the inclusion and exclusion criteria.

Intravenous, intramuscular or intra-articular corticosteroids: Intravenous or intramuscular corticosteroids are not permitted during the study. Intra-articular corticosteroids are not permitted within 6 weeks prior to baseline. Injection of intraarticular steroids while on blinded study medication is discouraged, but may be used in a limited fashion. No more than 1 joint per 24-week period may be injected during the core period of the study and should not be given 8 weeks or less before the Week 24 visit. No single injection should exceed 40 mg of triamcinolone (or equivalent).

6.4.3 Management of Specific Adverse Events or Adverse Drug Reactions

No specific measures are proposed for this trial. Standard medical care will be provided at the trial site for all AEs occurring during the trial.

6.4.3.1 Management of Latent Tuberculosis Infection Diagnosed During the Study

It is highly recommended to adhere to national/institutional guidelines to manage and treat subjects diagnosed as LTBI during the study.

Patients with a positive QFT at screening will be ineligible for the trial. Investigators may treat them per local/national guidance for LTBI outside of the study.

If a patient with a negative QFT during screening develops a positive QFT during the trial (ie, at Week 24), treatment with IMP should be stopped and an early termination visit completed. Such patients continue safety/immunogenicity visits (see Table 1 for schedule of assessments). The patient will return for a safety follow-up visit 4 weeks after the last dose of IMP and an additional safety evaluation visit 4 months after the last dose of IMP.

During this 4-week safety follow-up period no excluded treatment for RA (as defined in the protocol) should be administered. Patients will return for an additional safety follow-up visit 4 months after the last dose of IMP. Treatment for RA from the 4-week safety follow-up visit to the 4-month 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 the last IMP are completed within the 52-week visit schedule, these will not be repeated thereafter.

Patients who were QFT-negative at randomization but subsequently become QFT-positive at Week 24 should, at the safety follow-up visit (4 weeks after the last IMP administration), be referred by the Investigator for a consultation with an infectious disease specialist/pulmonologist as necessary in order to assess whether TB re-activation occurred during the trial.

Patients who were QFT-negative at randomization and at Week 24 but subsequently became QFT-positive at Week 52 should be referred by the Investigator for a consultation with an

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.

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.

The monitor will periodically collect the IMP accountability forms and will check all returns (both unused and used containers) before authorizing their destruction by the trial site. The preferred option is always to destroy used/unused medication at the trial site. Only in exceptional cases can the medication be returned to the Sponsor or designee for destruction.

6.8 Assessment of Investigational Medicinal Product Compliance

The IMP will be administered at the site on the trial visit days defined in Table 1. All other dosing will be done by the patient or patient's caregiver at home throughout the rest of the trial. Patients will be asked to record the date and time dispensed, date and time of dosing, location of administration, and injection site reaction (yes/no) in a patient diary. Diaries will be collected and reviewed at the trial visits specified in Table 1.

Patients will be instructed to bring all IMP, including the used packaging, to each trial visit to allow for the assessment of compliance with trial treatment. Prior to discharge from each scheduled visit, patients will be given sufficient IMP for at-home dosing until the next scheduled visit.

6.9 Blinding

This trial will be double-blinded. Blinding will be maintained throughout the trial duration, unless an emergency unblinding is necessary. In the event of a change in the reference product (eg, introduction in the market of the new 0.4 mL Humira® formulation) prior to the completion of this study, the sponsor will put in place a process to avoid any bias in the blinding. Randomization data will be kept strictly confidential, accessible only to authorized staff, until the time of unblinding. The trial blind may be broken for an individual only if knowledge of the IMP is essential for clinical management of an incurred SAE; however, unblinding is discouraged as knowledge of the treatment received has limited influence on the treatment of AEs. If the Investigator breaks the blind, he must contact the medical monitor immediately, and no later than 24 hours after performing the unblinding, without sharing any treatment assignment information. The Investigator must promptly explain the reason for any unblinding of an IMP to the Sponsor without revealing the result to any Sponsor employee except the designated Drug Safety representative. The Investigator must record the date of unblinding and the reason in the CRF. Under certain circumstances, Drug Safety may be required to unblind the treatment assignment for an individual patient following an SAE or other serious event; for example, if an expedited regulatory report is required. The CRO Medical Monitor will not break the blind.

All breaks of the trial blind must be adequately documented.

6.10 Emergency Unblinding

The trial blind may be broken for an individual only if knowledge of the IMP assignment is essential for clinical management of the patient. The Investigator must promptly explain the reason for any unblinding of an IMP to the Sponsor without revealing the result to any Sponsor employee except the designated Drug Safety representative (using the Emergency Unblinding Notification Form). The Investigator must record the date of unblinding and the reason in the CRF. Contact

information for breaking the blind in an emergency is given on the patient emergency card provided to each patient (see Section 9.4).

Under certain circumstances, Drug Safety may be required to unblind the treatment assignment for an individual patient following a serious adverse event (SAE) or other serious event; for example, if an expedited regulatory report is required. See Section 7.4 for further details on expedited reporting and SAEs.

6.11 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in a clinical trial protocol. In the event of an overdose, patients should receive appropriate supportive medical care and be followed until resolution/stabilization of any clinical issues.

Even if it does not meet other criteria for an SAE, any overdose must be recorded in the trial medication section of the CRF and reported to Drug Safety in an expedited manner using the appropriate reporting form, and following the procedure in Section 7.4.

6.12 Medical Care of Patients after End of Trial

The Sponsor will not provide any additional care to patients after they leave the trial. After patients leave the trial, medical care will be at the discretion of the Investigator following institutional standard of care.

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

Assessments during the trial will be performed according to Table 1. Patient reported outcome questionnaires must be performed prior to any other assessments at all visits. For volumes of blood collected, see Appendix C.

Prior to performing any trial assessments that are not part of routine medical care for the patient, the Investigator will obtain written informed consent as described in Section 9.2.

7.1.1 Screening Procedures and Assessments

The screening procedures will be completed within 28 to 3 days prior to drug administration.

The IWRS must be notified within 5 days of patients who fail screening. The following information, at a minimum, should be collected in the eCRF for patients who failed screening: informed consent, inclusion/exclusion criteria, basic demographics, reason for screen failure, AEs from the date of informed consent until patient is considered to have failed screening by the Investigator, and the Investigator's signature.

During screening, a serum β-human chorionic gonadotropin (β-hCG) pregnancy test will be performed for females of childbearing potential, and blood HIV, hepatitis B virus, and hepatitis C

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.

7.2.3 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.

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

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).

For DAS28-ESR, the 28 joints to be examined and assessed as tender or not tender for TJC and to be examined and assessed as swollen or not swollen for SJC include 14 joints on each side of the patient's body: 2 shoulders, 2 elbows, 2 wrists, 10 metacarpophalangeal joints, 2 interphalangeal joints of the thumb, 8 proximal interphalangeal joints, and 2 knees (58).

DAS28 will be derived using the following formulas from the DAS28 website (59):

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

Where:

- TJC28 = 28 joint count for tenderness
- SJC28 = 28 joint count for swelling
- ln(ESR) = natural logarithm of ESR
- GH = the general health component of the DAS (ie, Patient's Global Assessment of Disease Activity on a scale of 1 to 10 where 10 is maximal activity).

7.3.1.3 CDAI

The CDAI is calculated based on the following formula (46):

$$CDAI = SJC28 + TJC28 + GH + PGA$$

Where:

- TJC28 = 28 joint count for tenderness
- SJC28 = 28 joint count for swelling
- GH = the general health component of the DAS (ie, Patient's Global Assessment of Disease Activity on a scale of 1 to 10 where 10 is maximal activity).
- PGA = Physician's Global Assessment of Disease Activity on a scale of 1 to 10 where 10 is maximal activity

7.3.1.4 SDAI

The SDAI is calculated based on the following formula (46):

$$SDAI = SJC28 + TJC28 + GH + PGA + CRP$$

Where:

- TJC28 = 28 joint count for tenderness
- SJC28 = 28 joint count for swelling
- GH = the general health component of the DAS (ie, Patient's Global Assessment of Disease Activity on a scale of 1 to 10 where 10 is maximal activity).

- PGA = Physician's Global Assessment of Disease Activity on a scale of 1 to 10 where 10 is maximal activity
- CRP = C-reactive protein in mg/dL

7.4 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting, and analysis of baseline medical conditions, AEs, physical examination findings including vital signs and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by each patient will be performed from the time of giving informed consent and throughout the trial. The Investigator will report any AEs, whether observed by the Investigator or reported by the patient (see Section 7.4.2.2). The reporting period for AEs is described in Section 7.4.2.3.

7.4.1 Safety Monitoring Committee

An IDMC will review the safety data of this trial on ongoing basis (see Section 2). The IDMC is responsible for monitoring the safety of the trial participants and making appropriate recommendations based on the data reviewed. Details regarding the review process will be available in the relevant IDMC charter.

7.4.2 Adverse Events

7.4.2.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

Injection site pain during 3rd, 4th, and 5th injection administration will be reported as an AE similar to any injection site reactions at other time points of IMP administration.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the National Cancer Institute – Common Terminology Criteria for AEs (NCI-CTCAE), version 4.03 (publication date: 14 June 2010), a descriptive terminology that can be used for AE reporting.

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.)

- 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

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.

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.

8.2 Randomization

Eligible patients will be randomized in permuted blocks in a 1:1 ratio by an IWRS to receive either MSB11022-[redacted] s.c. or Humira® s.c. at a dose of 40 mg every other week starting at baseline up to and including Week 48.

Randomization will be stratified by previous disease-modifying therapy use. 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 1 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 (64, 65, 66).

8.3 Endpoints

8.3.1 Primary Endpoint

- Safety
  - Incidence of AESIs including and up to Week 52 (AEs will be recorded at each visit: screening, baseline [Week 0], and Weeks 2, 4, 8, 12, 24, 36, 48, and 52)

8.3.2 Secondary Endpoints

Key Secondary Endpoint

- Efficacy
  - ACR20 at Week 12

Other Secondary Endpoints

- Safety
  - Occurrences of TEAEs and SAEs including and up to the 4-month Safety Evaluation visit (AEs will be recorded at each visit: screening, baseline [Week 0], and Weeks 2, 4, 8, 12, 24, 36, 48, and 52, and 4-week and 4-month Safety Follow-up)
  - Vital signs at screening, baseline and at Weeks, 2, 4, 8, 12, 24, 36, 48, and 52
  - Physical examination at screening, baseline and at Weeks 2, 4, 8, 12, 24, 36, 48, and 52
  - Hematology, urinalysis and biochemistry analysis at screening, baseline and at Weeks 2, 4, 12, 24, 36, 48, and 52
  - ANA and anti-dsDNA at baseline and at Weeks 24 and 52
  - 12-lead ECG at screening, Weeks 12, 24, and 52

- 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.

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.

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.

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

to assist with the medical emergency and to provide support for the potential unblinding of the patient concerned.

9.5 Clinical Trial Insurance and Compensation to Patients

Insurance coverage will be provided for each country participating to the trial. Insurance conditions shall meet good local standards, as applicable.

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents, such as the ICF, to the responsible IEC or IRB for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File at the CRO.

The IEC or IRB will be asked to document the date of the meeting at which the favorable opinion or approval was given and the members and voting members present. Written evidence of favorable opinion or approval that clearly identifies the trial, the clinical trial protocol version and the Patient Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to this clinical trial protocol will also be submitted to the concerned IEC or IRB, before implementation of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC or IRB during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (for example, Investigational Medicinal Product Dossier, Patient Information and ICF) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

10 Trial Management

10.1 Case Report Form Handling

Refer to the Manual of Operations for CRF handling guidelines.

The main purpose of the CRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible, and timely manner. The data in the CRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this trial is accurate and documented appropriately on all applicable forms. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the CRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any patient names.

For PRO data such as QoL and pain assessments, ePRO and/or paper CRF will be used.

The data will be entered into a validated database. The Contract Research Organization will be responsible for data processing, in accordance with the Contract Research Organization data management procedures. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the CRFs will be provided to the Investigators after the completion of the trial.

10.2 Source Data and Patient Files

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every patient in the trial. It must be possible to identify each patient by using this patient file. This file will contain the demographic and medical information for the patient listed below and should be as complete as possible.

- Patient's full name, date of birth, sex, height, weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification, that is, the Sponsor trial number for this clinical trial, and patient number
- Dates for entry into the trial (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs
- Date that the patient left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

All documents containing source data must be filed, including, but not limited to CT or MRI scan images, ECG recordings, and laboratory results. Such documents must bear the patient number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

10.3 Investigator Site File and Archiving

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be archived include the Patient Identification List and the signed patient ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original patient files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH

GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH GCP and any other applicable regulations. The site Monitor will perform visits to the trial site at regular intervals.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be patient to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all trial documents and other materials at the site, including the Investigator Site File, the completed CRFs, all IMP and IMP accountability records, and the original medical records or files for each patient.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the patient's agreement to participate in the trial requires additional informed consent prior to implementation following the process as described in Section 9.2.

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the trial, a final clinical trial report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3.

10.6.2 Publication

The first publication will include the results of the analysis of the main endpoints and will include data from all trial sites that provided evaluable data. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.

Posting of data on ClinicalTrials.gov and the EU Clinical Trials Register is planned and will occur 12 months after the last clinic visit of the final trial patient or another appropriate date to meet applicable requirements.

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12. Appendices

Appendix A: Contraceptive Guidance and Woman of Childbearing Potential

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

1. Premenopausal female with one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

     Note: Documentation can come from the study site staff's: review of participant's medical records, medical examination, or medical history interview.
2. Premenarchal
3. Postmenopausal female
   - Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, an FSH will be drawn at screening.
   - Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraceptive Guidance

Highly Effective Contraceptive Methods That Are User Dependent Failure rate of < 1% per year when used consistently and correctly[a].

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  • oral
  • intravaginal
  • transdermal.

• Progestogen-only hormonal contraception associated with inhibition of ovulation
  • oral
  • injectable

Highly Effective Methods That Are User Independent
• implantable progestogen-only hormonal contraception associated with inhibition of ovulation • intrauterine device (IUD) • intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion.
• Vasectomized partner (A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)
• Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Appendix B: Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title:	A multicenter, randomized, double-blind, phase III trial to evaluate the safety, immunogenicity, and efficacy of MSB11022 compared with Humira® in patients with moderately to severely active rheumatoid arthritis
IND Number:	CCI [redacted]
EudraCT Number:	2016-002852-26
Clinical Trial Protocol Date / Version:	11 July 2017 / Version 2.0

Protocol Lead:

I approve the design of the clinical trial:

PPD _____ _____ PPD

Signature Date of Signature

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	Ares Trading S.A., an affiliate of Merck Serono S.A.
Address:	Z.I. de l'Ouriettaz, 1170 Aubonne, Switzerland
Telephone number:	PPD
E-mail address:	PPD

Signature Page – Coordinating Investigator

Trial Title	A multicenter, randomized, double-blind, phase III trial to descriptively evaluate the safety, immunogenicity, and efficacy of MSB11022 compared with Humira® in patients with moderately to severely active rheumatoid arthritis
IND Number	CCI
EudraCT Number	2016-002852-26
Clinical Trial Protocol Date / Version	11 July 2017 / Version 2.0

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

Name, academic degree: PPD

Function / Title: PPD

Institution: PPD

Address: PPD

Telephone number: PPD

Fax number: PPD

E-mail address: PPD

Signature Page – Principal Investigator

Trial Title	A multicenter, , randomized, double-blind, phase III trial to evaluate the safety, immunogenicity, and efficacy of MSB11022 compared with Humira® in patients with moderately to severely active rheumatoid arthritis
IND Number	CCI [redacted]
EudraCT Number	2016-002852-26
Clinical Trial Protocol Date / Version	11 July 2017 / Version 2.0
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also affirm that I understand that Health Authorities may require the Sponsors of clinical trials to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

Sponsor Responsible Persons not Named on the Cover Page

Name:	PPD
Function / Title:	Principal Clinical Trial Lead
Institution:	Merck KGaA
Address:	Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany
Telephone number:	PPD
E-mail address:	PPD

Name, academic degree:	PPD
Function/Title:	PPD
Institution:	PPD
Address:	PPD
Telephone number:	PPD
E-mail address:	PPD

Appendix C: Blood and Urine Volumes

Blood will be drawn on 12 separate days/occasions. On the day of PK/PD sampling, patients will have an intravenous catheter inserted to facilitate obtaining the multiple samples required. The planned maximum volume of blood to be drawn in this trial is approximately 390 mL over the screening period, 52-week trial period, 4-week follow-up period, and 4-month safety follow-up period (approximately 68 weeks total).

Assay	Approximate Sample Volume (mL)	Number of Samples[a]	Approximate Subtotal Volume (mL)
Clinical chemistry, hematology (blood sample)	7	9	63
Urinalysis	10	9	90
Antibody tests: ANA, anti-dsDNA (blood sample)	5	6	30
Pregnancy test (serum β-hCG) (blood sample)	3	1	3
Urine pregnancy test	5	11	55
Virus screen (HIV,HBV and HCV) (blood sample)	3.5	1	
QFT (blood sample)	3	1	3
High sensitivity C-reactive protein (blood sample)	3	8	24
Erythrocyte Sedimentation Rate (blood sample)	2	1	2
ADAs, NAbs (blood sample)	5	10	50
PK sample (blood sample)[b]	5	14	70
Total	**51.5**	**71**	**390**

ADA = anti-drug antibody; ANA = anti-nuclear antibody; β-hCG = beta human chorionic gonadotropin; dsDNA = double-stranded DNA; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; NAb = neutralizing antibody; PK = pharmacokinetics; QFT = QuantiFERON-TB Gold test.

a) Includes samples taken at screening or during double-blind period.

b) Blood for population pharmacokinetic assessment will be collected in a subset of 60 patients (30 per treatment arm). Patients in the population PK analysis will have additional samples 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). The date and exact time of sample collection must be recorded.

Appendix D: Joint Count Assessment Forms (66/68 Joint Evaluation)

	Patient Right						Patient Left					
	Pain/Tenderness			Swelling			Pain/Tenderness			Swelling		
JOINT[a] (Circle Correct Answer)	0 = Absent 1 = Present 9 = Not applicable[a]			0 = Absent 1 = Present 9 = Not applicable[a]			0 = Absent 1 = Present 9 = Not applicable[a]			0 = Absent 1 = Present 9 = Not applicable[a]		
1. Temporomandibular	0	1	9	0	1	9	0	1	9	0	1	9
2. Sternoclavicular	0	1	9	0	1	9	0	1	9	0	1	9
3. Acromio-clavicular	0	1	9	0	1	9	0	1	9	0	1	9
4. Shoulder	0	1	9	0	1	9	0	1	9	0	1	9
5. Elbow	0	1	9	0	1	9	0	1	9	0	1	9
6. Wrist	0	1	9	0	1	9	0	1	9	0	1	9
7. Metacarpophalangeal I	0	1	9	0	1	9	0	1	9	0	1	9
8. Metacarpophalangeal II	0	1	9	0	1	9	0	1	9	0	1	9
9. Metacarpophalangeal III	0	1	9	0	1	9	0	1	9	0	1	9
10. Metacarpophalangeal IV	0	1	9	0	1	9	0	1	9	0	1	9
11. Metacarpophalangeal V	0	1	9	0	1	9	0	1	9	0	1	9
12. Thumb Interphalangeal	0	1	9	0	1	9	0	1	9	0	1	9
13. Proximal Interphalangeal II	0	1	9	0	1	9	0	1	9	0	1	9
14. Proximal Interphalangeal III	0	1	9	0	1	9	0	1	9	0	1	9
15. Proximal Interphalangeal IV	0	1	9	0	1	9	0	1	9	0	1	9
16. Proximal Interphalangeal V	0	1	9	0	1	9	0	1	9	0	1	9
17. Distal Interphalangeal II	0	1	9	0	1	9	0	1	9	0	1	9
18. Distal Interphalangeal III	0	1	9	0	1	9	0	1	9	0	1	9
19. Distal Interphalangeal IV	0	1	9	0	1	9	0	1	9	0	1	9
20. Distal Interphalangeal V	0	1	9	0	1	9	0	1	9	0	1	9
21. Hip	0	1	9	N/A			0	1	9	N/A		
22. Knee	0	1	9	0	1	9	0	1	9	0	1	9
23. Ankle	0	1	9	0	1	9	0	1	9	0	1	9
24. Tarsus	0	1	9	0	1	9	0	1	9	0	1	9
25. Metatarsophalangeal I	0	1	9	0	1	9	0	1	9	0	1	9
26. Metatarsophalangeal II	0	1	9	0	1	9	0	1	9	0	1	9
27. Metatarsophalangeal III	0	1	9	0	1	9	0	1	9	0	1	9
28. Metatarsophalangeal IV	0	1	9	0	1	9	0	1	9	0	1	9
29. Metatarsophalangeal V	0	1	9	0	1	9	0	1	9	0	1	9
30. Great Toe	0	1	9	0	1	9	0	1	9	0	1	9
31. Interphalangeal II	0	1	9	0	1	9	0	1	9	0	1	9
32. Interphalangeal III	0	1	9	0	1	9	0	1	9	0	1	9
33. Interphalangeal IV	0	1	9	0	1	9	0	1	9	0	1	9
34. Interphalangeal V	0	1	9	0	1	9	0	1	9	0	1	9

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

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.

Amendment No. 2

Scope	Global
Date of Protocol Amendment	11 July 2017
Current Trial Protocol Version	11 July 2017/Version 2.0

Rationale

This global protocol amendment was prepared to include some clarifications and corrections in various sections, as well as to globally implement the changes which were requested by the PPD PPD (and implemented in the local protocol amendment 1) in order to conform pregnancy and contraception language to the Clinical Trial Facilitation Group guidelines and to remove an inadequate sentence from Section 6.9.

List of Changes

Changes were made to conform the language regarding pregnancy and contraception to Clinical Trial Facilitation Group guidelines and provide a new appendix regarding contraceptive methods.

Some sections of the clinical study protocol needed to be corrected as they were found inaccurate, and some other sections needed to be clarified.

Administrative and editorial changes were undertaken to correct typographical errors that do not impact the design or execution of the study.

Changes to the clinical study protocol text are presented in the table below. Additions and amended text are shown in bold. If the original clinical study protocol text was already bold, changes are shown in bold and underlined, deletions are marked using strike through.

Comparison with Clinical Study Protocol Version 1.0, 09 September 2016

Change	Section	Page	Previous Wording	New Wording
To update the number of sites and countries	Synopsis 2.0 Sponsor, Investigators and Trial Administrative Structure	9 21	Approximately ~~60~~ **50** trial sites in ~~8~~ **6** countries in ~~North America and~~ Europe.	Approximately 50 trial sites in 6 countries in Europe.
To update to the planned trial period	Synopsis	9	Planned trial period (first patient in-last patient out): First patient in: Quarter ~~IV 2016~~ **I 2017** Last patient out: Quarter ~~II~~ **III** 2018	Planned trial period (first patient in-last patient out): First patient in: Quarter I 2017 Last patient out: Quarter III 2018
To correct the alignment of PK objective and endpoints found in the synopsis and protocol body	Synopsis, 4.0 Trial Objectives	10, 26	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 evaluate population pharmacokinetics (PK) on MSB11022-CCI and Humira® in patients with moderately to severely active RA~~ • 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 MSB110220-CCI and Humira® in patients with moderately to severely active RA**	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

Change	Section	Page	Previous Wording	New Wording
	Synopsis	13	~~Population pharmacokinetics (PK)~~ • ~~Absorption rate constant (ka)~~ • ~~Apparent clearance (CL/F)~~ • ~~Volume of distribution (Vz/F)~~ • ~~C_{trough} levels at Day 14 after first dose, at Week 4, 12 and 24 pre-dose, and at Day 14 after dose of Week 24~~ Quality of Life • Health Assessment Questionnaire – Disability Index (HAQ-DI) questionnaire at screening, baseline, and Weeks 2, 4, 8, 12, 24, and 52 • 36-item Short Form Health Survey (SF-36) questionnaire at baseline and Weeks 12, 24, and 52 • Euro-Quality of Life – 5 Dimensions and 5-levels (EQ-5D-5L) questionnaire at baseline and Weeks 12, 24, and 52 Injection site pain • Mean change in injection site pain on a visual analog scale (VAS), evaluated during 3 administrations of IMP (doses 3 to 5) (immediately post-injection, 15 minutes post injection, and 1 hour post injection) **Exploratory endpoints** **Population pharmacokinetics (PK)** • **Absorption profile characterization, if it is supported by the data** • **Apparent clearance (CL/F)** • **Volume of distribution (Vz/F)** • **C_{trough} levels at Day 14 after first dose, at Week 4, 12 and 24 pre-dose, and at Day 14 after dose of Week 24**	Quality of Life • Health Assessment Questionnaire – Disability Index (HAQ-DI) questionnaire at screening, baseline, and Weeks 2, 4, 8, 12, 24, and 52 • 36-item Short Form Health Survey (SF-36) questionnaire at baseline and Weeks 12, 24, and 52 • Euro-Quality of Life – 5 Dimensions and 5-levels (EQ-5D-5L) questionnaire at baseline and Weeks 12, 24, and 52 Injection site pain • Mean change in injection site pain on a visual analog scale (VAS), evaluated during 3 administrations of IMP (doses 3 to 5) (immediately post-injection, 15 minutes post injection, and 1 hour post injection) Exploratory endpoints Population pharmacokinetics (PK) • Absorption profile characterization, if it is supported by the data • Apparent clearance (CL/F) • Volume of distribution (Vz/F) • C_{trough} levels at Day 14 after first dose, at Week 4, 12 and 24 pre-dose, and at Day 14 after dose of Week 24
	8.3.2 Secondary Endpoints	65	• Injection site pain • Mean change in injection site pain on a VAS, evaluated during 3 (doses 3-5) administrations of IMP • ~~Pharmacokinetics~~	• Injection site pain • Mean change in injection site pain on a VAS, evaluated during 3 (doses 3-5) administrations of IMP

Change	Section	Page	Previous Wording	New Wording
To align title and objectives with text describing evidence provided.	Synopsis, 5.2 Discussion of Trial Design	10, 27	This trial is a two-arm, randomized, multicenter, double-blind, parallel group trial designed to compare the **safety,** immunogenicity, ~~safety,~~ and efficacy of MSB11022-CCI with Humira® in approximately 260 randomized patients with moderately to severely active RA during a 52 week period.	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
	Synopsis	11	The 52-week double-blind period will allow for the collection of long-term comparative **safety,** immunogenicity, ~~safety,~~ and efficacy data for MSB11022-CCI versus Humira®.	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®.
	3.1 Adalimumab	22	The planned MS200588-0004 study will use this new CCI formulation and will offer supportive evidence by providing **safety,** immunogenicity, ~~safety,~~ and efficacy data in a major approved indication for adalimumab~~.~~**, RA**.	The planned MS200588-0004 study will use this new CCI formulation and will offer supportive evidence by providing safety, immunogenicity, and efficacy data in a major approved indication for adalimumab~~.~~, RA.
	5.2 Discussion of Trial Design	28	The 48-week double-blind treatment period will allow for the collection of long-term comparative **safety,** immunogenicity, ~~safety,~~ and efficacy data for MSB11022-CCI versus Humira®.	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®.
To clarify that analysis of the key secondary endpoint at Week 12 will be descriptive.	Synopsis, 5.2, Discussion of Trial Design	10, 27	**The** ~~P~~**p**rimary safety endpoint~~s~~ will be assessed up to Week 52, key secondary efficacy endpoint will be assessed at Week 12. ~~A descriptive analysis will be performed for the key secondary efficacy endpoint at Week 12 and the final analysis will be performed at Week 52~~**The analysis for the key secondary efficacy endpoint will be descriptive**.	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.
Addition of text to clarify that third dose of IMP will be administered on-site by the patient	Synopsis, 5.2 Discussion of Trial Design	11, 28	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~~. The next three~~ **for the remaining** doses. ~~of IMP (3-5) will be self-administered by the patient and i~~Injection site pain will be assessed **after doses 3 to 5**. 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**.	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. 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.

Change	Section	Page	Previous Wording	New Wording
To clarify that either of the 4-week and 4-month Safety Follow-up visits will not be duplicated if they fall within 2 weeks of a scheduled visit.	Synopsis, footnote c in Schedule of Assessments, Section 5.2 Discussion of Trial Design, Section 5.4.1 Withdrawal from Trial Therapy, Section 6.4.3.1 Management of Latent Tuberculosis Infection Diagnosed During the Study, Section 7.1.2 Baseline Assessments and Treatment Period	11, 18, 28, 39, 43, 49	The 4-week and 4-month Safety Follow-up **visits** will not be duplicated if ~~this visit~~ **either of these visits** falls within 2 weeks of an otherwise scheduled visit.	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.
To remove incorrect reference to neutralizing ADA titer	Synopsis	12	Immunogenicity • ADA to adalimumab and ADA titer including and up to Week 52 • Neutralizing ADA to adalimumab ~~and neutralizing ADA titer~~ including and up to Week 52	Immunogenicity • ADA to adalimumab and ADA titer including and up to Week 52 • Neutralizing ADA to adalimumab including and up to Week 52
To correct reference from Week 50 to Week 52	Synopsis, 8.3.2 Secondary Endpoints	12-13, 65	Efficacy • ACR20 at Weeks 2, 4, 8, 24, and ~~50~~ **52** • American College of Rheumatology 50% Response Criteria (ACR50) and American College of Rheumatology 70% Response Criteria (ACR70) at Weeks 2, 4, 8, 12, 24, and ~~50~~ **52** • Disease Activity Score based on a 28 joint count (DAS28)-ESR mean change from baseline at Weeks 2, 4, 8, 12, 24, and ~~50~~ **52**	Efficacy • ACR20 at Weeks 2, 4, 8, 24, and 52 • American College of Rheumatology 50% Response Criteria (ACR50) and American College of Rheumatology 70% Response Criteria (ACR70) at Weeks 2, 4, 8, 12, 24, and 52 • Disease Activity Score based on a 28 joint count (DAS28)-ESR mean change from baseline at Weeks 2, 4, 8, 12, 24, and 52

Change	Section	Page	Previous Wording	New Wording
			• Proportion of patients with low disease activity as measured by DAS28-ESR, and remission at Weeks 2, 4, 8, 12, 24, and ~~50~~ **52** • Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) mean change from baseline at Weeks 2, 4, 8, 12, 24, and ~~50~~ **52** • ACR/European League Against Rheumatism (EULAR) Boolean remission rates at Weeks 2, 4, 8, 12, 24, and ~~50~~ **52**	• Proportion of patients with low disease activity as measured by DAS28-ESR, and remission at Weeks 2, 4, 8, 12, 24, and 52 • Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) mean change from baseline at Weeks 2, 4, 8, 12, 24, and 52 • ACR/European League Against Rheumatism (EULAR) Boolean remission rates at Weeks 2, 4, 8, 12, 24, and 52
Removal of text to correct statement regarding PK analysis. This information will be provided in the PK statistical analysis plan.	Synopsis, Table 2 Population PK Table of Assessments footnote @, 5.2 Discussion of Trial Design, and 7.5 Pharmacokinetics, Appendix B (Appendix C in amended protocol) footnote b	13, 20, 29, 61, 87	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 ~~of Week 0~~, 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)**. ~~All PK samples will be included into the population PK analysis.~~	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).

<table>
<tr><th>Change</th><th>Section</th><th>Page</th><th>Previous Wording</th><th>New Wording</th></tr>
<tr><td rowspan="2">Edit of text to correct that the immunogenicity assessment will be analyzed using the Safety Analysis Set and to clarify the descriptive statistics.</td><td>Synopsis</td><td>15</td><td>Descriptive statistics of the immunogenicity assessment per treatment arm will be given with reference to the ~~ITT analysis set.~~Safety Analysis Set.</td><td>Descriptive statistics of the immunogenicity assessment per treatment arm will be given with reference to the Safety Analysis Set.</td></tr>
<tr><td>8.5.3.5 Analysis of Immunogenicity Endpoints</td><td>69</td><td>Descriptive statistics of the immunogenicity assessment per treatment arm ~~(ITT)~~ will be given with reference to the ~~ITT analysis set~~ 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 ~~an ADA result~~ a treatment period ≥ 6 months</td><td>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</td></tr>
<tr><td>Removal of non-applicable footnote.</td><td>Synopsis, Table 1 Schedule of Assessments</td><td>18</td><td><table><tr><th>Day/Week</th><th>W52[b]</th><th>ET[b]</th><th>4-week safety FU (4 weeks after last dose of IMP)[c]</th><th>4-month safety evaluation (4 months after last dose of IMP)[c]</th></tr><tr><td>Visit window (days)</td><td>± 2</td><td>± 7</td><td>± 7</td><td>± 7</td></tr><tr><td>Infectious disease specialist /pulmonologist consultation[v]</td><td>~~X~~[u] X</td><td></td><td>~~X~~[u] X</td><td></td></tr></table></td><td><table><tr><th>Day/Week</th><th>W52[b]</th><th>ET[b]</th><th>4-week safety FU (4 weeks after last dose of IMP)[c]</th><th>4-month safety evaluation (4 months after last dose of IMP)[c]</th></tr><tr><td>Visit window (days)</td><td>± 2</td><td>± 7</td><td>± 7</td><td>± 7</td></tr><tr><td>Infectious disease specialist /pulmonologist consultation[v]</td><td>X</td><td></td><td>X</td><td></td></tr></table></td></tr>
<tr><td>Modification of footnote i in Schedule of Assessments to match contraceptive guidance</td><td>Synopsis Schedule of Assessments</td><td>18</td><td>Follicle-stimulating hormone test will be performed to confirm postmenopausal status of women with continuous amenorrhea ~~for at least 2 years~~ ≥ 12 months.</td><td>Follicle-stimulating hormone test will be performed to confirm postmenopausal status of women with continuous amenorrhea ≥ 12 months.</td></tr>
</table>

Change	Section	Page	Previous Wording	New Wording
To correct the list of approved indications for Humira	3.1 Adalimumab	22	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 colitis, plaque psoriasis, pediatric plaque psoriasis (EU only), ~~and~~ pediatric Crohn's disease ~~and~~**,** hidradenitis suppurativa**, and uveitis**.	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 colitis, plaque psoriasis, pediatric plaque psoriasis (EU only), pediatric Crohn's disease, hidradenitis suppurativa, and uveitis.
Modification of inclusion criteria as per the request from PEI	5.3.1 Inclusion Criteria	34-35	8. **A female patient is eligible to participate if she is not pregnant (see Appendix A), not breastfeeding, and at least one of the following conditions applies:** ~~Women of childbearing potential must use highly effective methods of contraception to prevent pregnancy for 4 weeks before randomization and must agree to continue to practice adequate contraception for 5 months after the last dose of IMP~~. ~~For the purposes of this trial, women of childbearing potential are defined as all female patients after onset of puberty unless they are:~~ a. **Not a woman of childbearing potential (WOCBP) as defined in Appendix A** ~~Postmenopausal, defined by continuous amenorrhea for at least 2 years and confirmed by follicle-stimulating hormone at screening, or~~ **OR** b. **A WOCBP who agrees to use a highly effective contraception (ie, methods with a failure rate of less than 1% per year) as detailed in Appendix A of this protocol 3 months before the start of the first dose of the IMP, during the treatment period, and for at least 5 months after the last dose of the IMP.** ~~Surgically sterile (tubal ligation is acceptable as a method of surgical sterilization if it has been performed at least 1 year prior to screening without reversal)~~	8. A female patient is eligible to participate if she is not pregnant (see Appendix A), not breastfeeding, and at least one of the following conditions applies: a. Not a woman of childbearing potential (WOCBP) as defined in Appendix A OR b. A WOCBP who agrees to use a highly effective contraception (ie, methods with a failure rate of less than 1% per year) as detailed in Appendix A of this protocol 3 months before the start of the first dose of the IMP, during the treatment period, and for at least 5 months after the last dose of the IMP. 9. Female patients must not be pregnant and if of childbearing potential, must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline before randomization. 10. Female patients must not be lactating or breast-feeding at screening through at least 5 months after the last treatment with IMP.

Change	Section	Page	Previous Wording	New Wording
			~~Highly effective contraception is defined as use of 2 barrier methods (eg, female diaphragm and male condoms) or 1 barrier method with spermicide or an intrauterine device or hormonal contraceptives (eg, implant, injectable, patch or oral*), or total abstinence from intercourse (when this is in line with the preferred and usual lifestyle of the patient).~~ ~~*If contraception is oral, patients should have been stable on the same contraceptive pill for a minimum of 3 months before initiation of trial treatment.~~ 9. ~~Women~~ **Female patients** must not be pregnant and if of childbearing potential, must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline before randomization. 10. ~~Women~~ **Female patients** must not be lactating or breast-feeding at screening through at least 5 months after the last treatment with IMP. 11. Male patients must be either surgically sterile (vasectomy with documented confirmation of aspermia) or **must agree to use a condom and have their female partners use a highly effective contraception (ie, methods with a failure rate of less than 1% per year) as detailed in Appendix A for 3 months before the first dose of IMP, during the treatment period and for at least 5 months after the last dose of IMP, unless their partners are infertile or surgically sterile. Male patients must agree to continue to practice adequate contraception for 5 months after the administration of the IMP and refrain from donating sperm during this period.** ~~willing to use a condom in addition to having their female partner use another form of contraception (such as an intra-uterine device, barrier method with spermicide, or hormonal contraceptive [eg, implant, injectable, patch or oral]), unless their partners are infertile or surgically sterile.~~	11. Male patients must be either surgically sterile (vasectomy with documented confirmation of aspermia) or must agree to use a condom and have their female partners use a highly effective contraception (ie, methods with a failure rate of less than 1% per year) as detailed in Appendix A for 3 months before the first dose of IMP, during the treatment period and for at least 5 months after the last dose of IMP, unless their partners are infertile or surgically sterile. Male patients must agree to continue to practice adequate contraception for 5 months after the administration of the IMP and refrain from donating sperm during this period.
Clarifying what items the patient should be expected to receive with their IMP.	6.6 Preparation, Handling, and Storage of the Investigational Medicinal Product	45	Patients should have access to refrigeration to store the IMP. Patients will also receive sharps containers and handling instructions ~~and leaflets~~.	Patients should have access to refrigeration to store the IMP. Patients will also receive sharps containers and handling instructions.

Change	Section	Page	Previous Wording	New Wording
Removal of 1 sentence asking the Investigator to contact the medical monitor for unblinding, as per the request from PEI.	6.9 Blinding	46	The trial blind may be broken for an individual only if knowledge of the IMP is essential for clinical management of an incurred SAE; however, unblinding is discouraged as knowledge of the treatment received has limited influence on the treatment of AEs. ~~The Investigator should attempt to contact the medical monitor to discuss in advance the possibility of unblinding.~~ If the Investigator breaks the blind, he must contact the medical monitor immediately, and no later than 24 hours after performing the unblinding, without sharing any treatment assignment information.	The trial blind may be broken for an individual only if knowledge of the IMP is essential for clinical management of an incurred SAE; however, unblinding is discouraged as knowledge of the treatment received has limited influence on the treatment of AEs. If the Investigator breaks the blind, he must contact the medical monitor immediately, and no later than 24 hours after performing the unblinding, without sharing any treatment assignment information.
Clarification of the overdose definition by removal of an incorrect sentence.	6.11 Treatment of Overdose	47	An overdose is defined as any dose greater than the highest daily dose included in a clinical trial protocol. ~~Any dose taken outside of ±2 days of the schedule will qualify as overdose for the next dose.~~ In the event of an overdose, patients should receive appropriate supportive medical care and be followed until resolution/stabilization of any clinical issues.	An overdose is defined as any dose greater than the highest daily dose included in a clinical trial protocol. In the event of an overdose, patients should receive appropriate supportive medical care and be followed until resolution/stabilization of any clinical issues.
Addition of text to clarify where the IMP doses will be given for the first 3 doses and by whom.	7.1.2 Baseline Assessments and Treatment Period	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 ~~2~~ **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.	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.
Addition of text to clarify assay validation sampling.	7.2.4 Immunogenicity	50	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).	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).
Clarifying that CRP and not high-sensitivity CRP will be detected as part of the SDAI.	7.3.1.4 SDAI	53-54	SDAI = SJC28 + TJC28 + GH + PGA +~~hsCRP~~ **CRP** Where: • TJC28 = 28 joint count for tenderness • SJC28 = 28 joint count for swelling • GH = the general health component of the DAS (ie, Patient's Global Assessment of Disease Activity on a scale of 1 to 10 where 10 is maximal activity).	SDAI = SJC28 + TJC28 + GH + PGA + CRP Where: • TJC28 = 28 joint count for tenderness • SJC28 = 28 joint count for swelling • GH = the general health component of the DAS (ie, Patient's Global Assessment of Disease Activity on a scale of 1 to 10 where 10 is maximal activity).

Change	Section	Page	Previous Wording	New Wording
			• PGA = Physician's Global Assessment of Disease Activity on a scale of 1 to 10 where 10 is maximal activity • ~~hsCRP~~ **CRP** = ~~high sensitivity~~ C-reactive protein in mg/dL	• PGA = Physician's Global Assessment of Disease Activity on a scale of 1 to 10 where 10 is maximal activity • CRP = C-reactive protein in mg/dL
To more accurately define absorption endpoint	8.3.3 Exploratory Endpoints	65	• Pharmacokinetic endpoints from a population PK analysis • Absorption ~~rate constant (ka)~~ **profile characterization, if it is supported by the data**	• Pharmacokinetic endpoints from a population PK analysis • Absorption profile characterization, if it is supported by the data
	8.5.4 Analysis of Population Pharmacokinetic Endpoints	69	Pharmacokinetic parameters (absorption ~~rate constant~~ **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.	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.
Inadvertent inclusion of PP safety analysis set, which will not be part of the data analyses.	8.4.3 Per-Protocol	66	~~Two PP populations will be described, one for efficacy, the other for safety assessment.~~ 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.	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.
Addition of text to specify covariate analysis of PK parameters.	8.5.4 Analysis of Population Pharmacokinetics Endpoints	69	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.**	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.

Change	Section	Page	Previous Wording	New Wording
Addition of Contraceptive Guidance following the request from PEI	Appendix A Contraceptive Guidance and Woman of Childbearing Potential	82	**Definitions** **Woman of Childbearing Potential (WOCBP)** **A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.** **Women in the following categories are not considered WOCBP** **1. Premenopausal female with one of the following:** • **Documented hysterectomy** • **Documented bilateral salpingectomy** • **Documented bilateral oophorectomy** **Note: Documentation can come from the study site staff's: review of participant's medical records, medical examination, or medical history interview.** **2. Premenarchal** **3. Postmenopausal female** • **Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, an FSH will be drawn at Screening.** • **Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.** **Contraceptive Guidance** **Highly Effective Contraceptive Methods That Are User Dependent**	**Definitions** **Woman of Childbearing Potential (WOCBP)** A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. **Women in the following categories are not considered WOCBP** 1. Premenopausal female with one of the following: • Documented hysterectomy • Documented bilateral salpingectomy • Documented bilateral oophorectomy Note: Documentation can come from the study site staff's: review of participant's medical records, medical examination, or medical history interview. 2. Premenarchal 3. Postmenopausal female • Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, an FSH will be drawn at Screening. • Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment. **Contraceptive Guidance**

Change	Section	Page	Previous Wording	New Wording
			Failure rate of < 1% per year when used consistently and correctly[a].	**Highly Effective Contraceptive Methods That Are User Dependent** Failure rate of < 1% per year when used consistently and correctly[a].

			• **Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation**
			  • **oral**
			  • **intravaginal**
			  • **transdermal.**
				• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
				  • oral
				  • intravaginal
				  • transdermal.

			• **Progestogen-only hormonal contraception associated with inhibition of ovulation**
			  • **oral**
			  • **injectable**
				• Progestogen-only hormonal contraception associated with inhibition of ovulation
				  • oral
				  • injectable

			Highly Effective Methods That Are User Independent	**Highly Effective Methods That Are User Independent**
			• **implantable progestogen-only hormonal contraception associated with inhibition of ovulation** • **intrauterine device (IUD)** • **intrauterine hormone-releasing system (IUS)** • **bilateral tubal occlusion.**	• implantable progestogen-only hormonal contraception associated with inhibition of ovulation • intrauterine device (IUD) • intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion.
			• **Vasectomized partner** **(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used).**	• Vasectomized partner (A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used).
			• **Sexual abstinence** **(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)**	• Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMP. The reliability of
			NOTES: **a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of**	

Change	Section	Page	Previous Wording	New Wording
			contraceptive methods for participants participating in clinical studies.	sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.) NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.